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THE COMMON COLD AND ALLIED UPPER RESPIRATORY INFECTIONS

OBSERVATIONS DURING THE FIVE-YEAR COURSE OF THE SELF-SELECTION DIET STUDY

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DURING the five and one-half years in which a study of the self-selection of diet by newly weaned infants was under way, a rather unique opportunity was afforded for the observation of colds, sore throats, etc., in vigorous, healthy children from infancy to five years of age, living under uniform and precisely known conditions of environment and diet.

The cold, a nuisance and menace in the community, is common indeed in occurrence but uncommonly difficult to study intensively, especially in the milder forms so prevalent among small children. Experienced mothers do not, as a rule, call the doctor for every "sniffle" or sore throat their children may have, and it is chiefly the more severe ones and the complications of these that receive medical attention. Moreover, the circumstances of family life lend themselves but poorly to the detailed study of the occurrence of minor respiratory infections, let alone their relations, if any, to habits, diet and weather, investigation of which in our present state of incomplete knowledge of the etiologic factors may be worth while.

Carried on as this dietary study was, without significant change in its methods during the five years and with a fairly homogeneous group of sixteen children all taken in infancy and continuing in residence for periods ranging from six months to four and one-half years, re-

spectively, it provided two prime requisites for a clinical study of this sort:

1. Daily medical and trained nursing observation of the children, and

2. Complete records as follows:

a. Daily charts showing weight, temperature, stools, and any deviations from normal, e.g., even a slight and transient nasal discharge.

b. Results of monthly physical examinations and complete blood counts and hemoglobin estimations (Sahli method) and biweekly urine examinations.

c. Daily record, by meals, of the amounts in weighed or measured quantities of each food eaten at each meal.

d. Weather bureau records of daily outdoor temperature, humidity, barometric readings, and hours of sunshine; and, during the last year, records of indoor temperature and humidity.

The daily food records and the statistics derived from them are of particular interest in view of the present wide discussion of the rôle of nutrition in general and certain of its factors in particular, in the preventon of colds and sinus infections.

There was one important exception to the general uniformity of experimental conditions, viz., the locus of the experiment, so that with respect to this, the experiment falls naturally into two periods:

1. The first two years, in which it was carried on in the children's ward of a general hospital where a large percentage of the patients were children ill with pneumonia or the prevalent complications of upper respiratory infections, and where the infants were never outdoors except in the summer time on a shaded porch.

2. The following three and one-half years, when fifteen children (including two of those from the previously mentioned hospital group) lived in a modest city house transformed through private generosity into a small institution solely for the purposes of the dietary study and where conditions more nearly approached those of family life. In good weather the children played in the yard or went to the park. The nursemaids held them, played with them, and the affectionate relations between children and staff were of the wholesome everyday sort, so that nothing in the behavior of these children suggested that they had been "institutionalized." Adult contacts (staff and visitors) were naturally more numerous than in the usual home, and no family, of course, could have at one time so many children under the age of five years. These factors in exposure to colds were offset, however, by the complete absence of contacts with children outside of the institution, for none played with other children than those in the nursery, or went to school or kindergarten, or entered other houses.

Three children when eight to ten days old were taken into the nursery for the purpose of a study in the self-selection of feeding for-

mulas,* and were kept in a room of their own, two of them being put at weaning age with the other children, all of whom were breast-fed infants taken at weaning age, i.e., when from six to eleven months old.

The first, or hospital period of the experiment may be briefly summarized. The three infants kept in the hospital were admitted during fall or winter months and two had mild head colds, apparently little more than a "sniffle" when admitted. All three infants, despite every care of nursing and medical staff, had acquired before two weeks of hospital stay had elapsed, a severe upper respiratory infection, with a thick, yellow nasal discharge that poured out in quantity and showed no tendency to clear up spontaneously, or with treatment, until an adenoidectomy was performed. All had fever and rather severe constitutional symptoms with these upper respiratory infections and, as complications, two had mild suppurative otitis media, the other, spontaneous rupture of an eardrum with a thin serous discharge for a day, and one, an antrum infection, suspected at the time but not proved until long after.

After adenoidectomy, the few colds these infants had were of the same character as to nasal discharge and constitutional symptoms, but recovery was spontaneous, though slow, and the colds were without complications. The mild "three-day cold" with no greater inconvenience to the infant than a running nose, however, was conspicuously absent.

This experience bears out the common view emphasized so well by Chapin and Brennemann, that the hospital ward is a dangerous place for well infants and young children and that the colds contracted in it are apt to be infections of a more virulent type than are the common colds of home life.

During the three and one-half years of the second, or nursery period of the study, no colds of this hospital type were seen among its fifteen infants and small children. Mucous nasal discharges or mucopurulent ones in which mucus greatly predominated were the rule, and colds ran a short and acute course to spontaneous and complete recovery without complications or extensions save when coincident with another known infection or contagious disease.

For the purposes of this report, the colds and sore throats of the three-and-one-half-year nursery period (15 infants and runabouts) have been classified on a purely clinical basis, as follows:

I. Mild Colds	38
II. Moderately Severe Colds	26
III. Acute Catarrhal Tonsillitis	17
IV. Acute Follicular Tonsillitis	7
V. Acute Streptococcus infection (Contact)	1

*Results not yet reported.

There were no cases of laryngitis, tracheitis, bronchitis, or pneumonia, either primary or as complications or sequelae of colds.

I. MILD COLDS

Thirty-eight colds were classified as "mild" on the basis of symptoms, signs, temperature, character of nasal discharge, and duration. The children apparently did not feel ill or out of sorts, and played with their usual zest, objecting loudly to having to stay in bed, and rarely lying down except for their usual nap and night sleep. The temperature range (rectal) was commonly from 99.6° to 100.5° F., although in a few instances, temperatures between 100.5° and 101° F. were recorded once, usually on the day of onset. Noses ran freely for from two to four days and occasionally a slight, intermittent discharge was seen for another day or two. The discharge was watery at first and mucoid throughout, without yellow or greenish color, and, although a reddened pharynx was the rule, there was neither cough nor evidence of sore throat. A few cases in this group showed a "dromedary" (or, more properly, "camel") type, of course, having two distinct episodes, similar in every respect, but separated from each other by three or four days with a dry nose and normal temperature. These Group I colds corresponded in every respect to the mild colds of family life as described by Holt and Howland[1] under the heading, "Coryza or Acute Nasal Catarrah." They were rarely, if indeed ever, transmitted to the adult personnel, nor were we able to definitely trace their origin to adult contacts, although the outbreak of such colds on several occasions within forty-eight hours after visits of outsiders to the nursery may possibly have occurred in the same way as the outbreaks of colds among the Eskimos after fresh contacts with outsiders reported by Heinbecker and Irvine-Jones.[2]

II. MODERATELY SEVERE COLDS

The criteria for the classification of a cold as "moderately severe" were: (1) fever of 101° F. (rectal) or higher for at least one day; (2) evident malaise, usually of a degree such that the child remained in bed for one or more days without much protest; (3) a yellowish or greenish, mucopurulent nasal discharge. The greater number of these colds lasted but three to five days, but in a few instances a nasal discharge was present in slight amounts for almost two weeks. The slight cough that was often present for two or three days was neither distressing nor persistent. Of the twenty-six colds in this group, eighteen occurred in two epidemics, in January and March of 1929, simultaneously with outbreaks of similar colds (commonly called "grippe") in the community at large. The January epidemic was

initiated by an adult member of the personnel, and in the March one the onset in the children and in one adult was on the same day. The eight remaining cases of this group of moderately severe colds occurred in some of the children at times when others had only mild colds.

In connection with these cases of frank colds, nothing is as interesting, perhaps, as the occurrence in the three and one-half years of fifty-five cases of what we have tentatively called "colds below the usual threshold of diagnosis." These were characterized by one or more of the following symptoms listed in order of their frequency: a temperature of from 99.5° to 100.5° F. (rectal), a slightly reddened pharynx, and, in some, an intermittent slight watery nasal discharge, seen but two or three times in the course of a day or two. This discharge might easily have passed for that seen after crying or after being out in cold and wind had not the circumstances of its occurrence been observed, and the cases would have been overlooked had it not been for the daily routine of temperature taking and throat inspection and the careful reexamination of all the children, regardless of the time of day, upon the first appearance of a cold in any individual in the group. In all these cases it was difficult to decide whether the child had a cold or not and conclusive proof that these were truly colds is admittedly lacking, but we believe that they were colds, differing only in degree from the mild Group I colds since (1) they occurred when and only when others among the children had frank colds and although carefully looked for could not be found during months in which the nursery was wholly free from frank colds; and (2) because within two or three days after their occurrence, small palpable cervical glands could usually be found where none were palpable before. It is perhaps such colds as these to which the more observant mothers refer when they say, "I thought my baby was going to have a cold, but he didn't," or, "The baby had a little sniffle for a day, but it did not amount to anything." In many homes, however, they may easily come and go without being noticed. The occurrence of such mild or abortive cases, at or below the usual threshold of definite diagnosis, in certain of the contagious diseases and their epidemiologic importance is, of course, well recognized, and it may be that a similar situation obtains with colds. In fact Dochez and his coworkers[3] in their experimental study of colds have reported reddening of the throat with swelling of lymph follicles after inoculation with their filtrate, lasting about twenty-four hours, without definite symptoms of infection; but in reporting their results on the production of colds by inoculation say, "In spite of these slight changes the results have been considered negative."

III. AND IV. TONSILLITIS

Acute catarrhal and acute follicular tonsillitis occurred seventeen and seven times, respectively, nine cases being in one epidemic. In the catarrhal cases the duration never exceeded three days while about half of the follicular cases lasted a day or two longer before full recovery from all signs and symptoms.

V. UNCLASSIFIED

One case of upper respiratory infection could not be properly classified under any of the above headings. This occurred in R. L., a six-week-old infant. She was cared for and fed one night by a night nurse who went on duty feeling well but who, after going off duty the following morning, became suddenly ill with a sore throat, chill, and temperature of 104.0° F. (oral). In the course of a few hours a streptococcic exudate *(Streptococcus hemolyticus)* covered both tonsils, and this was followed in a few days by pneumonia. Forty-eight hours after the nurse went off duty, R. L. was slightly fretful and had a slight fever that persisted for four days without nasal discharge, red throat, or other signs of illness on physical examination. Then, after a three-day interval of normal temperature, she again had fever, this time with reddened ear drums and, within twenty-four hours, a bilateral suppurative otitis media, the pus from the ears yielding a pure culture of *Streptococcus hemolyticus.*

It seems probable that the initial febrile period was due to a streptococcus infection of adenoid tissue rather than to an ordinary cold of which there were no signs or symptoms.

COMPLICATIONS

Excluding the unclassified case mentioned above, as probably one of contact streptococcus infection without preceding cold, the complications and sequelae of colds and tonsillitis were four in number. Of these, three occurred in infants under one year of age, who had had mild colds during the incubation period of acute glandular fever of Pfeiffer (November, 1928, epidemic) or during convalescence from it. One had a suppurative otitis media, the other two suppuration of a single cervical gland. It may be questioned whether these were not complications of the acute glandular fever, since Pfeiffer in his original description includes otitis media and suppuration of glands among the complications; but the fact that these three children were the only ones who had colds during this period and also the only ones having these complications, although all the children in the nursery had glandular fever, inclines one to the view that the complications were due rather to the coincidence of the two infections.

The fourth complication, or rather, sequela, was a parotid abscess that followed acute follicular tonsillitis in a year-old boy who, three days prior to the onset of the tonsillitis, had been visited by his mother. She, as we subsequently learned, had had all her teeth extracted the day before her visit, for dental abscesses and pyorrhea, and at the time of her visit had a very sore mouth with exudate on the gums. There was no other case of tonsillitis in the nursery for two months before or after this one.

Common colds and tonsillitis had, then, in this series of cases, neither complications nor sequelae, except (a) when children had both a cold and an acute contagious disease and (b) when a child had had close contact with an adult having a purulent infection of the mouth or tonsils.

The total child occupancy of the nursery for the three-and-one-half-year period was three hundred and eighty-six months. There were, therefore, one moderately severe cold for each 14.9 months' occupancy; one mild cold for each ten months' occupancy; one case of follicular tonsillitis for each three and one-half years' occupancy, and one of catarrhal tonsillitis for each two and one-quarter years' occupancy. These rates of incidence probably differ little from those obtaining among children living in average homes.

MANAGEMENT OF COLDS

Naturally, in a nursery of this kind we were eager to do everything possible to lessen the incidence of colds and, if possible, to shorten their duration when present; but while we spared no efforts along these lines, the results, if any, were meager and too uncertain to bear critical examination. Visitors having colds were not admitted, and personnel with colds were not allowed on duty until nasal discharge had disappeared. All eating utensils—spoons, dishes, and glasses—were boiled fifteen minutes after each meal, as carefully when all were well as when some had colds. Children were confined to bed under precautions on the appearance of the first symptom of a cold, and those with colds segregated from the well. But, since it happened not infrequently that colds appeared in all either on the same day or within forty-eight hours after the first was observed, no great success attended these measures. It is, of course, possible that with older children, instead of toddlers and creepers, in whom occurs a maximum of putting commonly used toys in the mouth when together in a playroom, such measures are more productive of results.

Prophylactic treatment according to a well-known English practice,[4] viz., the instillation of a drop or two of a 10 per cent solution of argyrol, or of a solution of zinc sulphate, gr. i to the ounce of water, in either eye of all children in the nursery as soon as the first sign of

a cold was observed in any one of them, was tried from September, 1929 to June, 1930. The record for that winter (the middle one of the three) shows fewer colds than for either of the others, but was not enough better to warrant any conclusions. The method was abandoned in June, 1930.

In the treatment of the colds themselves, five varieties of drops for intranasal use were given a fairly thorough trial, viz.:

1. Argyrol or neosilvol, 10 per cent solution
2. Camphor and menthol in albolene (common formula)
3. Mercurochrome, 2 per cent solution
4. Potassium permanganate, solution 1:7500
5. Ephedrine, 1 per cent in oil, or in a jelly with menthol, etc.

Without exception all caused some discomfort and the use of the first four seemed definitely to increase and prolong nasal discharge and pharyngeal irritation, nor could we discover any particular difference of one from another in the effects of their use. The same could also be said for the *routine* use of the ephedrine preparations, although in cases with more than usual nasal obstruction its usefulness in securing better nasal drainage and easier nasal breathing apparently overbalanced the discomfort of a nasal instillation. The use of the first four was ultimately wholly abandoned and that of the ephedrine compounds limited to special cases. We are also of the impression that watery solutions of ephedrine caused less discomfort as a rule than those in oil, and were more efficacious.

Aspirin, or a solution of sodium salicylate with potassium citrate, in the customary dosages, were usually given, our impression being that children with fever and general malaise were commonly made more comfortable thereby but that in mild colds there was no discernible effect and little, if any, reason for their use.

Adenoidectomy was performed in two cases, both in children who when admitted had large adenoids as evidenced by mouth-breathing and quality of voice, and whose frequent slight nasal discharge was always placing them under suspicion of having colds. None of the children had large tonsils, and tonsillectomy was not performed on any child.

During the course of colds and tonsillitis the children were allowed, regardless of the height of fever, to continue choosing their foods as usual without restrictions of any kind, either as to articles or quantities. We were thus able to observe the manner in which children naturally regulate their diet in acute illness of this sort and soon found that the uniformity of their eating behavior under such circumstances was such that the dietitian could base her marketing upon it, when colds were epidemic at the nursery. Appetites were adversely affected by these upper respiratory infections in proportion to the severity of

the general symptoms, i.e., fever, prostration, malaise, and/or discomfort in swallowing with an inflamed throat. In mild (Group I) colds where these symptoms were lacking, the decrease in appetite was practically negligible and discernible only when a number of these children had such colds at the same time and the total quantity of food eaten by the group fell noticeably, as the decrease in the calories of individuals was usually within the limits of normal variation. Decrease in appetite began from twelve to twenty-four hours *before* any signs of "cold" could be detected by physical examination and, when noted, made possible the correct prediction of such illness among the children. This decrease of appetite as a prodromal symptom is well known and would not be mentioned here were it not for the fact that in the moderately severe (Group II) colds a sharp increase in appetite occurred from twelve to twenty-fours hours before the fall in temperature or improvement in signs, making possible the equally correct prediction of convalescence on the next day. This prognostic rebound of appetite before amelioration of fever and other signs of illness is often obscured or missed in the hospital and in the home by the practice of giving light diets and "invalid foods" until after the temperature has dropped to normal, but in these children it was clearly shown that the appetite curve antedated in its fall and rise, the rise and fall of the temperature curve, the changes in it occurring *pari passu* with the subjective feelings of illness or recovery experienced by the child, rather than with the physical signs that could be elicited by examination. It was interesting and amazing to see a young child whose temperature was 103° F. and who for a day or two had shown little interest in his food, suddenly sit up when his tray came in and eat heartily and with enjoyment of meat, potatoes, and vegetables, asking for second and third helpings, and to find that no disturbance of digestion resulted. The same relation of appetite curve to fever curve was seen in the nursery epidemic of acute glandular fever of Pfeiffer and has since been observed in hospital children ill with acute infections when allowed the regular house diet throughout the illness.

Regardless of the variety of likes displayed by the children when well, during convalescence from upper respiratory infections all ate large quantities of raw beef, beets, and usually, carrots. Indeed, children who never ate raw beef at other times did so during convalescence, and the increased demand for all three articles of food when colds were epidemic made it necessary for the dietitian to order extra quantities of them. Since a moderately severe cold or tonsillitis often caused a temporary drop in the red cell count of from 200,000 to 500,000 with a corresponding lowering of hemoglobin percentage, the demand for raw beef may probably be explained on this basis, but as yet no explanation is evident for the increased appetite for beets.

As stated before, the temporary deficit in calories, due to the acute illness, was promptly made up, and there were no instances of poor appetite after a cold.

RELATION OF WEATHER CONDITIONS TO THE INCIDENCE OF COLDS

A discussion of the incidence of colds can hardly afford to ignore the question of weather conditions and, of these, the region of the Great Lakes and Chicago, the locale of the nursery, offers a maximum variety in this country according to the United States Weather Bureau. For this reason, the United States Weather Bureau's daily reports on Chicago weather for the three and one-half years of the nursery's existence have been studied, as well as the record of temperature and humidities in the nursery made in the last year. Tycos thermometers and hygrometer were used and readings were made at 7 A.M., 12 M., and 5 P.M., daily. During the season of artificial heat, daytime temperatures were at approximately 68 to 70° F., and at night, the usual temperature range was from 55 to 65° F. Fresh, outside air was constantly provided by a simple type of window ventilator, and cheap humidifiers on the radiators maintained a relative humidity that varied little from 48 to 54.

The seasonal variations in the prevalence of colds are, of course, well recognized and, as might have been expected, the incidence of colds at the nursery afforded no exception to common experience in this respect.

Half of the total number of colds occurred in the two calendar periods, September 15 to November 15 and the months of February and March, and had the nursery been carried on through the winter months of 1931-32 to the completion of its fourth year, so that the period covered as many winters as summers, the proportion would probably have been even greater. The seasonal variations in both incidence and severity is even more striking if the record for the four months that in this climate may properly be called "summer" be compared with that of the remaining portion of the year as in Table I.

TABLE I

PERIOD		MODERATELY SEVERE COLDS		MILD COLDS
May 15 – Sept. 15	4 yr.	(16 mo.)	1	3
Sept. 15 – May 15	3½ yr.	(25 mo.)	25	35

Of the group designated as "colds below the usual threshold of diagnosis," six occurred in the summer season and forty-nine in the winter months.

Careful correlation of the calendar of colds with the Weather Bureau's daily reports of temperatures, barometric pressure, relative

humidities, precipitation, hours of sunshine, and wind direction and velocity, failed to disclose any relation between any of these weather factors, taken singly, and the occurrence of colds. Cloudy intervals were no more prolific of colds than were sunny; even when a deficiency of hours of sunshine had accumulated over a period of several weeks; and extremes of cold, of wetness, of high wind, or sudden changes in the temperature, occurring singly were, only in rare instances, either coincident with or closely precedent to an outbreak of colds. But, although no evidence was forthcoming that any one of these factors bore any relation in time to the incidence of colds in the nursery, it was found that a combination of some of them in a certain direction was usually followed by an outbreak of colds. This combination was: high winds (gales) accompanied by sudden drops in temperature and in barometric pressure, resulting in major storms (usually with rain or snow), i.e., storms for which the Weather Bureau had issued storm warnings. In the years in question, all but a few of such major storms occurred from mid-September to mid-November, or the February-March periods, i.e., in the two peak seasons of incidence of colds. This may be merely a coincidence of these few years, but it is interesting to recall in this connection the exacerbation of symptoms experienced by many rheumatic patients in connection with such storms.

Many interesting theories have been brought forward from time to time to account for the seasonal incidence of colds, but, as in the cases of other diseases whose incidence varies regularly with the season, the bald fact still stands in need of elucidation since, obviously, from the standpoint of preventive medicine, it is more than a little important to know whether the seasonal influences that make for high incidence are exerted chiefly on the etiologic agent or on the host, or on both.

RELATION OF INDIVIDUAL HEALTH, NUTRITIONAL STATE, AND DIET TO THE INCIDENCE OF COLDS

The failure, thus far, of all efforts to discover the basic reasons for the seasonal variation in the incidence of colds, and to identify a virus or other infectious agent, together with the brilliant successes that have attended nutritional studies in recent years, especially in the field of the vitamins, has quite properly led to a reexamination of the question of colds from the point of view of individual health, nutrition, and diet, and the center of interest has shifted somewhat from the infectious agent to the condition and dietary habits of the host. With the many reports appearing in the literature of the rôle of adequate nutrition, and particularly of vitamin A, in the prevention of sinus and other respiratory infections in laboratory animals, it seemed worthwhile to go over the individual food records, and records of physical and laboratory examinations and daily notes and weights, with a view

to discovering the relation, if any, between the health, nutritional state, and diet, and the incidence of colds, in this unusually closely observed and carefully documented group of children who were under study for periods ranging in the different individuals from six months to four and one-half years (average two and one-eighth years).

To make a comparison between the incidence of colds among children in good health and those in poor health is not possible in this study for the reason that there were none with chronic infections, rheumatism, digestive difficulties, or other diseases of chronic and health-impairing course, and as the acute illnesses other than colds and tonsillitis were limited to epidemic acute glandular fever of Pfeiffer and mild attacks of acute pyelitis that occurred in the first three months of nursery residence in three infants whose urine contained a moderate number of leucocytes when admitted. It can only be said that the good health and vigor of these children did not appear to offer any greater protection against colds and tonsillitis than such good health commonly does against the ordinary contagious disease.

The five infants who were underweight and poorly nourished when admitted to the nursery began at once to gain weight and within four months were as healthy and well nourished as the others. Hence, no comparison can be made in this study between the incidence of colds in well-nourished and chronically undernourished children of the same group, and certainly no evidence is forthcoming from it that excellence of the general nutritional state (as judged by present standards) is in any measurable degree a preventive of colds and tonsillitis. There is, of course, nothing surprising in this since it is a matter of common observation that many apparently well-nourished and vigorous children have frequent colds while some who appear frail and undernourished go for periods of months or years without one, for reasons that are not easily apparent but might conceivably lie in the proportions of the various factors that make up the diet, or in slight unrecognized deficiencies of some of the more recently discovered ones.

The circumstances of this study where the same foods were provided for all but the choice of foods left to each individual resulted in a wide variation in choice of food among the children. Some ate only negligible quantities of vegetables throughout their nursery stay; others ate everything in a way that would have delighted the most anxious mother's heart. It thus became possible to examine the widely different diets chosen by individuals for a possible correlation with the incidence of colds among them, the interest of such an examination being enhanced by the fact that some children had almost twice as many colds as others.

The records of the calories, proteins, fat, and carbohydrate, per kilogram of body weight per day were first carefully scrutinized in

connection with the records of each individual's colds. The calories per kilogram of body weight per day continued their inexorable decline at an ever slowing rate of speed from the age of weaning on, in strict accordance with the well-known laws of metabolism, and in all children alike, regardless of the diet chosen or how few or many were their colds, and the incidence of colds among those who were the largest and those who were the smallest eaters (highest and lowest calories per kilogram per day) was practically the same, while the calories per kilogram per day of the three children who had the most colds were close to the average for the group.

Protein per kilogram of body weight per day was higher in all cases than the figures commonly accepted as covering the requirements of children of this age (i.e. above 2.0 gm.), the lowest for any child for any six-month period being 2.34 gm. and the highest, 6.17 gm., both being in periods that covered the first six months after weaning; fat and carbohydrate showed a 100 per cent variation from lowest to highest (fat: 2.84 gm. to 5.74 gm.; carbohydrate: 6.53 to 14.43 gm.), but the variations in these, whether from time to time in the same individual, or as between different individuals, bore no discoverable relation to the incidence of colds.

Naturally, however, at this time when the drama of "the little things" in diet and nutrition is being unfolded before our very eyes and the vitamins loom larger and larger in medical literature and in advertising propaganda, interest centers in the possible rôle of these food factors and, more particularly, in the fat-soluble ones, A and D, in the prevention of colds, rather than in protein and calories. Moreover, we have been unconsciously prepared for belief, or at least hope, in their efficacy since long before the vitamins were known an increased susceptibility to colds was postulated for the rachitic infant, and the practice of giving cod liver oil to children at least throughout the fall and winter months, in the hope of lessening the incidence of colds, had become more or less generally established—a practice that, as we now know, insured the child's receiving considerable amounts of vitamin A as well as of vitamin D. Finally, the reports of the prevalence of sinus infections, otitis, mastoiditis, and pneumonias among laboratory animals fed on rations deficient in vitamin A and the rôle of that vitamin in maintaining epithelial health and integrity have further raised our hopes for the usefulness of a fat-soluble factor in the control of upper respiratory infections, such as the common cold and sore throat.

Fortunately, simple clinical tests are available for determining the presence or absence in the diet, as actually eaten, of amounts of these vitamins adequate for protection in their respective antirachitic and antiophthalmic capacities, viz., roentgenographic examination and direct

examination of the cornea. But, if these vitamins have specific capacity, either singly or together, as preventives of colds and sore throats, the dosage in which they are effective is not a matter of common knowledge. Certainly the question of whether the incidence of children's colds has been lessened by the giving of cod liver oil is still a moot one when so keen a clinical observer as Brennemann[5] writes, "I have prescribed barrels of cod liver oil, and still do, but have never been able to convince myself in a situation in which control is impossible that it has a demonstrably beneficial effect in the prophylaxis of respiratory infection, except in so far as it removes a cause of lowered resistance by preventing and curing rickets in infancy." With regard to the dietary factors, vitamins A and D, it is my intention to give here merely the facts observed and the limited conclusions that can be drawn from them.

Of the nursery children, all nine who were well nourished at the time of weaning and beginning the self-selection of their diet were free from either clinical or roentgenologic signs of rickets, regardless of whether they had been given cod liver oil during the nursing period or not. Of the five received in an undernourished condition, one had severe florid rickets with badly bowed legs, one mild rickets (clinically and roentgenologically) and three, slight rickets revealed only by the routine roentgenograms made at the time of admission. These latter, like the others, received no cod liver oil, viosterol, sun baths, or ultraviolet ray treatments, but roentgenograms showed healed rickets in all cases within four months after admission regardless of the season of year at which they were admitted. Presumably, therefore, they received from their foods without the use of vitamin-D-supplying adjuvants an adequate amount of that vitamin not only to maintain normal bone structure during growth but also to permit healing of active rickets. The incidence of colds in these children and in the nine who had had no rickets was practically the same (actually 0.36 less per six-month period for those who had had rickets). Similarly, the incidence of colds in those (six) who had been given cod liver oil regularly throughout their nursing periods, in those who had had it irregularly (two) and in those who had never had any (six) was almost identical. A.B. and R.G., for example, who were well nourished and had had cod liver oil from the first month on until weaned, had the highest incidence of colds, while P.C., who had also had cod liver oil throughout his nursing period but who was poorly nourished and had severe florid rickets, was the only child who went as long as thirteen months without an upper respiratory infection. E.W., who had the lowest incidence of colds for her entire nursery stay (three and one-half years), had never had cod liver oil and was poorly nourished with mild active rickets on admission.

In this small group, therefore, no evidence was forthcoming that the dietary intake of vitamin D in amounts adequate for normal de-

velopment of bone and healing of rickets had preventive value against upper respiratory infection.

The number of units of vitamin A actually received by these children during the respective six-month periods of their nursery stays cannot be computed at this time since determinations of the vitamin A content of certain of their foodstuffs have not as yet been made. But as foods rich in vitamin A (liver, eggs, kidneys, carrots, etc.) were eaten by many in amounts far in excess of those even available to a majority of well-fed children, and as no sugar, "incomplete," canned, or preserved foods were on the diet list, they could hardly have escaped taking a diet richer in all the vitamins, including A, than that of the average well-conditioned child. The study, however, fails to show any relation between the amounts of vitamin-A-rich foods eaten by the different children and the incidence of colds among them, and of the two who frequently showed carotenemia of a marked degree, one (A.B.), was one of the two with the highest incidence of colds.

It would seem, therefore, that if vitamins A and D have specific prophylactic value against the common upper respiratory infections, it can only be in doses much larger than those required for optimal growth (A) and normal bone development (D). The failure of Hess, Lewis, and Barenburg,[6] Barenburg and Lewis,[7] and Wright, Frosst, Puchel, and Lawrence[8] to find any protective value of these vitamins (and particularly of vitamin A) in their experimental work with large doses as dietary adjuvants discourages, to say the least, an undue optimism as to their specificity in any dosage.

Inasmuch as quantitative determinations of the various minerals in bone marrow and in some of the glandular organs used in the diet have not yet been made available by research workers on the chemistry of foods, nothing can be said at this time regarding a possible correlation between the intake of minerals, either as a whole or as individuals, and the incidence of upper respiratory infection, but it is perhaps worth noting in view of the advertising propaganda for "alkalinization of the body" by diet and the use of alkalies both for the prevention and cure of colds, that a positive alkaline dietary balance of two to one was among these children the rule to which there was only a rare exception for one or two periods, and that the children whose dietary alkaline balances were the greatest throughout the study fared no better than the others in the incidence of colds.

COMMENT

This study then has disappointingly failed to disclose any relation between a number of dietary factors (including vitamins A and D) and the incidence of colds in this carefully documented group of young children observed over a relatively long period of time, and in so doing appears to run counter not only to the results obtained by much animal

experimentation especially with vitamin A, but also to the commonly entertained idea that healthy, well-fed children should not have colds, and that, if they do, there is something wrong with their diet or nutritional state. Naturally the results of this study are not conclusive, nor need the case for the importance of diet in this connection stand or fall by the results of the quest for cold-preventive ones among its many factors. What happens to a child, once he has "taken cold" or has a sore throat is after all a question of major importance for him and for his family, and, if it can be shown that good nutrition in general or individual dietary factors exercise specific functions in preventing serious extensions and complications and in lessening the severity and duration, in short, in reducing the cold from a menace to a nuisance, then diet may at least be relied upon to render comparatively harmless what it cannot prevent.

One would like to think that the mildness of the colds in this nursery, their short duration, the absence of complications of any sort except when a cold and a contagious disease were coincidental, and the quick rebound to unabated health, appetite, and vigor, were due to the excellent nutritional state of these children, and hence to diet. But an element of uncertainty creeps in when one considers the differences in character and duration of the colds seen in the hospital ward and nursery periods of this study, the variant in the two periods being environmental and not nutritional. With this in mind it would seem to the writer, as to Barenburg and Lewis, that adequate supplies of all the known dietary factors, and a good nutritional state are, so far as this class of illness is concerned, only contributors to that general "resistance" to infection, in the maintenance of which at a high level, adequate rest, good hygiene, and favorable environment also play their part, as may also conceivably such internal factors as speedy and precise functioning of the heat-producing and regulating mechanism of the body in the various extremes of temperature and combinations of weather conditions, and finally "maturation," which replaces in our present-day medical terminology the homely old way of saying that children have a tendency to "outgrow" their susceptibility to many infections including, often, colds and tonsillitis.

Deficiencies of rest, environment, and hygiene, which we have been accustomed to designate more precisely as "fatigue," "exposure" to wet and cold, and "crowding under unsanitary conditions," have long been known to have much similar effects on the character, severity, duration, and outcome of respiratory infection, as have some dietary deficiencies in general and quite probably vitamin A in particular, especially if such deficiencies are more or less chronic. If a high level of resistance to infection tends to reduce the common upper respiratory infections from a menace to a nuisance, contributory dietary factors are not to be despised.

SUMMARY

1. The paper presents an intensive study of colds and tonsillitis in a group of healthy young children living in a nursery under carefully controlled and recorded conditions of diet and hygiene.

2. Seasonal occurrence was the outstanding feature of the incidence of colds in this group as it is in the community at large.

3. Evidence that either incidence or severity bore any relation to a dietary factor or factors was not forthcoming.

4. The occurrence of colds so mild as to be below the usual threshold of diagnosis is reported.

5. The preventive and therapeutic measures used in the nursery and their results are discussed.

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HEMOPHILUS PERTUSSIS ENDOANTIGEN (KRUEGER)

USE IN 122 CASES

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DURING a recent whooping cough epidemic in the village of Winnetka, Ill., and surrounding communities, Krueger's endoantingen[1] was used in the treatment of 122 active cases and exposures.

The antigen used represented from forty-five to fifty billion organisms per 100 c.c. and was supplied for clinical trial by the Eli Lilly Company, Indianapolis, Ind.

Previous reports of the use of this antigen in California have been made by J. M. Frawley et al.[2, 3] Their conclusions indicate that the antigen has merit both as a prophylactic and therapeutic measure in the treatment of pertussis. They report that among twenty-one children having pertussis who received treatment 76 per cent had mild attacks. Among another group of 165 cases, eighty-six of whom had the antigen within one week after onset, 59 per cent had mild, 19 per cent moderate, and 12 per cent severe attacks. In a second group who received the vaccine later than one week after onset, mild attacks occurred in 45 per cent, moderate in 43 per cent, and severe in 10 per cent. Among a third group of 614 children who received the antigen as a prophylactic measure, 12 per cent of the vaccinated group and 10 per cent of the unvaccinated group developed whooping cough. However, 62 per cent of the vaccinated group had mild attacks, and only 12 per cent of the unvaccinated group had mild attacks.

At this point a comparison of the figures from epidemics in which the usual pertussis vaccine was used may be of value. Madsen's last report on the use of this vaccine in the Faroe Islands[4] is interesting in this respect. He found that among 1,832 vaccinated individuals 25.4 per cent did not develop the disease and 73.4 per cent had mild attacks. Among 446 unvaccinated individuals 1.8 per cent did not develop pertussis and 50.4 per cent had mild attacks. Madsen believes that the favorable results indicated by these figures are due to three factors: (1) the vaccine was made from young strains; (2) the dose used was large (total twenty-two million bacteria); and (3) vaccination was completed shortly before the onset of the epidemic.

Aldrich[5] in 1925 reported a series of cases also taken from an epidemic in Winnetka, Ill., in which, although percentage figures are not avail-

able, a *B. pertussis* vaccine was used with favorable results. Other men have made similar observations. Frequently the opinion is expressed that pertussis vaccine is of no value either in the treatment or prophylaxis of pertussis. Sauer's[6] recent work may belie the latter statement.

During the current epidemic, 122 children received the endoantigen either for prophylaxis or treatment of pertussis. Our method of administration varied from that of Frawley in that we began with 0.5 c.c. of the antigen and administered two doses of 1 c.c. on alternate days thereafter. Each child received a total of 2.5 c.c., this amount representing the antigen from one and one-half billions *Hemophilus pertussis* bacilli. The method of administration is identical to that used when the regular *B. pertussis* vaccine was given in previous epidemics.

An estimation of the effectiveness of treatment in pertussis is difficult, for epidemics vary in their severity; individual response to infection varies; and a mistaken diagnosis of pertussis is not an uncommon error. Certain individuals, as indicated by Siebler and Okrent,[7] seem to have a natural immunity to the disease. The effectiveness of our report is lessened by the lack of a control group.

ANALYSIS OF CASES

In an attempt to secure as accurate a picture as possible of each case in which the antigen was used, all were charted in the following manner:

Sex____ Age____ Stage antigen was administered____ Duration of cough____
No. of paroxysms a day (average)____ No. of vomitings a day (average)____
No. of night paroxysms (average)____ No. of night vomitings (average)____
Abatement after vaccine?____ Complications____
Nourishment, general conditions____ Remarks____

As each case terminated the mother was carefully questioned, following the above outline. This information together with our own observations made during the course of the disease enabled us to secure a fairly graphic picture of the clinical course of the disease among these children.

Following completion of the survey made upon the 122 children who received the antigen, the cases were divided into four separate groups.

Group A. Children who were exposed but did not contract pertussis.
Group B. Mild cases.
Group C. Moderate cases.
Group D. Severe cases.

Analysis of Group A.—(Children who were exposed but did not contract pertussis.)

All of this group of children had definite exposure to known active cases of pertussis and many had close and repeated exposures. In four

instances brothers or sisters had active cases. Twenty-five, or 55.5 per cent of forty-five children who received the antigen before onset of the cough, did not develop pertussis. Each of the twenty-five children received the antigen within seven days after exposure. This percentage of protection is twice that reported by Frawley, but 5 per cent less than that reported by Madsen. If we allow for those who may have had a natural immunity or for other factors which may have had some part in prevention, our figure for prophylaxis probably would be lower.

Analysis of Group B.—(Mild cases. Total number, fifty-six; male, thirty-five, and female, twenty-one.)

The average duration of cough was four and four-tenths weeks; longest period, six weeks; and shortest period, five days.

Thirty-three children had cough for only four weeks or less.

Twenty-five per cent of the children were under four and one-half years of age. Twelve and five-tenths per cent of the children were over ten years of age. Sixty-two and five-tenths per cent of the children were between four and ten years of age.

Forty-eight children (85.7 per cent) had the antigen following onset of cough. Eight (14.3 per cent) had the antigen during the incubation period.

Twenty-five (44.6 per cent) had no vomiting. The remainder had a very mild type of vomiting, averaging from one to three times in twenty-four hours and continuing only from one to four days.

Thirteen (23.2 per cent) did not whoop. One child who had been whooping stopped entirely two days following the third dose of the antigen.

Seven (12.5 per cent) had as high as ten paroxysms in twenty-four hours. Two children had as high as fifteen, and, among all of these, the paroxysms continued for only a short time (from five to seven days).

I believe that no one can doubt that most of these cases were a very mild type of pertussis. Complications occurred in two instances: In one a mild capillary bronchitis; and the other an acute otitis media.

Analysis of Group C.—(Moderate cases. Total number, seventeen: male, six, and female, eleven.)

The average duration of cough was 5.5 weeks, longest period, eight weeks; shortest period, three weeks. (The child who coughed for 8 weeks at no time had a severe cough.)

Forty-one per cent of the children were under four and one-half years of age. None were over eight years.

Seven (41.1 per cent) had antigen following onset of cough. Ten (50.8 per cent) had antigen before onset of cough.

Four (23.5 per cent) had no vomiting. Whooping occurred in all cases (100 per cent). Thirteen (76.5 per cent) had ten or more

paroxysms in twenty-four hours. Five (29.4 per cent) had fifteen or sixteen paroxysms in twenty-four hours. Two (11.7 per cent) had as high as from twenty to twenty-four paroxysms in twenty-four hours, but one of these entirely stopped coughing at the end of the third week of the disease.

Complications occurred in one instance. This child for two weeks had a daily fever ranging from 100° to 101° F. for which no cause could be detected other than the pertussis infection.

Several of the moderate group possibly could have been included in the mild group. We prefer to err on the side of pessimism.

Analysis of Group D.—(Severe cases. Total, twenty-four cases: male, eleven, and female, thirteen). The average duration of cough was 5.6 weeks; longest period, six weeks; shortest period, four weeks.

Thirty-seven and five-tenths per cent were under four and one-half years of age. Sixty-two and five-tenths per cent were between four and one-half and nine years.

Nineteen (79.1 per cent) had the antigen following onset of cough. Five (20.8 per cent) had the antigen during the incubation period.

Vomiting occurred in twenty-one cases (87.5 per cent). However, among these, only four vomited more than five times in twenty-four hours. Three (12.5 per cent) did not vomit.

Whooping occurred in all cases (100 per cent). The fewest paroxysms in twenty-four hours were nine, and the highest number, forty. Ten children had as high as twenty paroxysms on some days. One child for a few days had as high as thirty paroxysms in twenty-four hours. Severe cough continued for a greater period than two weeks in only four instances. Six children had a severe cough for only one week.

Complications occurred in five instances:

1. Four short convulsions in twenty-four hours. Stopped and did not recur following calomel purge. No residual effect.
2. Mild capillary bronchitis.
3. Repeated epistaxis (not severe).
4. Bilateral internal strabismus.
5. Enlargement of bronchial glands.

GENERAL CONSIDERATIONS

There were only four children one year of age or less in the group. One avoided the disease entirely; one had a mild attack; one, a moderate; and the fourth, a short severe attack.

Of twenty children who received the antigen before the onset of the cough and later developed pertussis, fifteen (75 per cent) had mild or moderate attacks.

A total of forty-five children received the antigen for known exposure. Twenty-five (55.5 per cent) did not develop pertussis.

Among the mild cases, twenty-one (37.5 per cent) received antigen seven days or less following onset of cough; thirty-six (64.3 per cent) ten days or less following onset.

Of the seventeen moderate cases, four (23.5 per cent) received antigen seven days or less following onset of cough; nine (52.9 per cent), ten days or less.

Among the twenty-four severe cases, five (20.8 per cent) received antigen seven days or less following onset of cough; nine (37.5 per cent), ten days or less.

In thirty-six instances (37.1 per cent) mothers reported definite abatement of the cough within from twelve to twenty-four hours following injection of the antigen. Because of this fact, six of the more severe cases received repeated doses of the antigen during the severe part of the paroxysmal stage, and all but one of these experienced definite abatement of the cough for a day or two following each injection.

SUMMARY AND COMMENT

One hundred and twenty-two children received pertussis endoantigen either for treatment or prophylaxis of whooping cough.

Fifty-five and five-tenths per cent of forty-five children who received antigen for known exposure did not develop pertussis. Among those who developed pertussis, 75.2 per cent had moderate or mild attacks (57.7 per cent mild). Twenty-four and seven-tenths per cent had severe attacks. Eighty and three-tenths per cent of all children receiving the antigen either did not have or had moderate or mild attacks of pertussis. Sixty-six and four-tenths per cent either did not have pertussis or had very mild attacks.

The average duration of all cases including mild, moderate, and severe was 5.16 weeks. This is a relatively short period for a winter epidemic.

General reactions to the antigen did not occur. Local reactions were small and of no consequence. There were no serious complications and no deaths.

Our experience indicates that the antigen probably is of most value when given before the onset of the cough; or if the cough has begun, within less than seven days following onset. In some instances, there was a favorable response when the antigen was given late in the attack.

The antigen treatment probably will be of still greater value if it is administered in larger and more numerous doses.

CONCLUSIONS

Experience with the use of Krueger's *Hemophilus pertussis* endoantigen (122 children received the preparation) indicates that the majority of children who receive the antigen will have mild attacks of pertussis. Although the prophylactic effect is more uncertain, the antigen apparently has the definite effect of modifying and shortening a majority of pertussis infections. This fact is particularly true when the antigen is given early in the attack or before onset of the cough.

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723 ELM STREET

PERTUSSIS IN ADULTS

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IN A RECENT epidemic of pertussis, chronic coughs in adult contacts were sufficiently common to suggest a study of the cases to determine whether or not *B. pertussis* was an etiologic factor.

While the literature postulates the existence of adult pertussis, there is agreement that it is rare. This opinion is based chiefly on the fact that the disease is highly communicable and that usually one attack protects. One article[7] states that only 2.5 per cent of cases are in persons over the age of fifteen years. The following quotation is from *Oxford Medicine* (Vol. 5, p. 820): "Often older children and adults develop persistent coughs without any definite paroxysms and whoops, which are probably mild grades of whooping cough."

Three articles[3, 8, 10] found in the German literature spoke of the atypical picture, stressing the importance of this fact epidemiologically. Hennes[3] states that his four children contracted whooping cough from an adult suffering from the disease, also that he himself contracted it in an atypical form. He finds pertussis in adults often unrecognized because of the absence of the typical stridor and believes these cases are often responsible for the spread of the infection among children. Neurath[8] finds adult pertussis less severe than juvenile, the adult type being characterized by a laryngeal cough without hoarseness and the tendency to spasmodic cough being unconsciously repressed below the characteristic type. This repression may be absent in neurotic individuals, allowing the juvenile picture to appear. Schwenkenbecher[10] describes an epidemic of pertussis which ran through a connecting group of five offices. Only a few developed the characteristic whoop, but all had a severe cough and catarrhal affection, persisting in some for several months. The disease was carried into the families of these patients. He protests against the assumption that pertussis is a children's disease, although stating that the symptoms in adults are generally so slight and of so little significance that they are overlooked.* Luttinger[6] in the summary of his thorough survey of the epidemiology of pertussis in New York City states, "Adult pertussis carriers probably have been disseminating the disease and have remained unrecognized owing to the atypical form in which it manifests itself."

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*"Die Erkrankung ist eben bei Erwachsenen in der Regel so leicht und so wenig eindeutig, dass sie übersehen wird."

Regarding the immunology of pertussis there is much evidence to indicate that the popular belief in the rarity of second attacks of pertussis is erroneous. Pfaundler and Schlossmann[9] say, "It is possible that a child may become affected with pertussis a second time—an interval of complete health extending over years precluding a relapse of the first affection—but in such an event the course of the disease is rapid and light." Luttinger[6] found eighteen among 9,400 with an apparent second attack of whooping cough with a typical whoop. Barbour[1] has ". . . . seen many adults who had pertussis, some of them very severe cases." Smith[11] gives a detailed history of a case of a second attack occurring in a girl of thirteen years who had had pertussis at the age of four; he also states, "I have seen a few instances in which mothers of children with pertussis developed a modified second attack, and Widowitz records seven instances of second attacks of the disease in individuals over thirty years of age." Bayer[2] gives case histories of recurrences but would be very critical of the other reported cases, requiring that they meet the following criteria: (1) a sufficiently long interval between the attacks, (2) that both attacks be typical, and (3) that in both attacks there should be a lymphocytosis. Furthermore, by analogy with other diseases, such as measles and smallpox, which are known to confer a high degree of immunity, but yet in which there are many well-authenticated cases of second attacks on record, it is obvious that the existence of an "absolute immunity" is extremely unlikely.

The adults represented in this study were those found in a two-month survey of the cases coming into the juvenile pertussis clinics at University of California Hospital and Children's Hospital, San Francisco. It does not include all the cases, since unavoidably some individuals will not cooperate.

PROCEDURE

A thorough history covering all the anticipated characteristics was taken on all adults presenting themselves with a chronic cough. This was supplemented by careful follow-up notes. Blood counts were taken when the patients were first seen and periodically from every two to five days during the clinical course. Cough plates were taken when feasible and after adequate incubation thoroughly examined bacteriologically. A positive cough plate means that typical colonies were isolated and the organism identified morphologically and by agglutination.

ANALYSIS OF CASES

Thirty-two cases were followed for variable periods. Twenty-nine were adults, aged twenty-four years or more, the other three being children of five, twelve, and fifteen years with histories of previous pertussis.

Of the twenty-nine cases of chronic cough in adults, nine had a history of previous pertussis; thirteen had a history of no previous pertussis; and seven had a history which was questionable although all thought they had had it.

Eight of the twenty-nine cases were males, the other twenty-one females. This fact probably was accounted for on the basis of closer contact.

As most of the patients were in continued contact with pertussis, it is difficult to state the incubation period with any degree of accuracy. However, by taking the time of clinical onset in the transmitter as the date of exposure, one arrives at an approximate incubation period. In sixteen of the cases, the date of onset of the case to which exposed is known and by averaging the incubation periods thus figured, we find it to be 14.5 plus days with a low of seven and a high of twenty-three days. These figures correspond very well with those for the incubation period in juvenile pertussis as usually stated, i.e., from seven to twenty-one days. As summarized by Jones[4]: "The period of incubation in pertussis seems to vary considerably. Intervals ranging from three days to five weeks have been reported. Fourteen days is commonly regarded as the average."

The duration of symptoms varied from twenty-four to over eighty days, averaging over six weeks.

Many patients noted one or more of those factors which are found to precipitate coughing spells. Exertion in one form or another was most common, with temperature changes, eating, and drinking, the other factors noted in children, less frequently mentioned.

In only four of the cases was the symptom of tickling in the throat absent.

Night cough was present in every case and was worse at night at some period in the clinical course in all except four cases. The cough was just a chronic hacking without paroxysms in six cases, the rest having periods of paroxysms superimposed on the chronic hacking cough. In only two cases was the cough definitely not productive, most of the remainder having the typical heavy, thick, tenacious, white or yellowish phlegm, while a few had a loose phlegm. In one case the sputum was definitely blood tinged on several occasions.

The symptoms of whooping, vomiting, and gagging or choking with the coughing paroxysms showed a wide variation in severity and duration. Some individuals had none of the three; some had just gagging or choking; some had an occasional whoop or slight emesis of phlegm; and some had all three symptoms to a marked extent, being clinically comparable with a severe case of juvenile pertussis.

It was noted early that the coughing was sufficient to bring on muscle soreness. The pain was most frequently noted along the costal margins at the origins of the abdominal muscles. This symp-

tom, a good indication of the severity, frequency, and duration of the cough, was present in half of the adults.

Bacteriology.—In six cases the bacteriologic proof by cough plate was conclusive; in two others "pertussis-like" organisms were found without successful complete isolation.

More bacteriologic proof was not obtained for various reasons, principally because of difficulty with the media. At the time the study was made we were experimenting with various media and the results in typical cases of juvenile pertussis were often unsatisfactory.

Epidemiology.—There were two instances in this series in which the onset in the adult preceded the onset of typical pertussis in the child by eight and nine days, respectively. The danger of adult pertussis is worth emphasizing as a disseminator because of the apparently mild innocuous course.

Immunology.—While the data are not conclusive because of the absence of cough plates in the first attack, the indication is very strong that second attacks of pertussis are more frequent than commonly assumed. There were nine cases in which the history of previous pertussis was positive, in three of which the cough plate in the second attack was positive and the clinical course was of the mild atypical form. There were also the three children spoken of above, in whom the second attack came within the childhood period.

Blood Findings.—A number of studies of the blood in juvenile pertussis have been made. A recent paper by Thelander and his coworkers[12] reviews the literature and presents graphically the findings. Characteristically, a rise in the total blood count due chiefly to the lymphocyte fraction begins from five to fifteen days after the onset of symptoms, continues to a maximum height in eight or ten days and then recedes gradually to normal, the entire elevation extending over a period of from twenty-five to thirty days.

No careful studies have been made of the blood in adult pertussis. In this series, therefore, counts were taken on the first visit and from every two to five days thereafter during the clinical course. Superficially most of the counts obtained were normal, both with respect to the total count and the differential percentages. However, a number of the lymphocyte percentages were in the thirties or above; 30 per cent being considered the upper limit of normal. Most of the counts were within the usual limits of from 5,000 to 10,000. Therefore, when the gross findings are considered, it is seen that many exhibited a relative lymphocytosis. In addition, there were occasional counts which exhibited absolute lymphocytosis.

When curves were plotted, a fall was found in the absolute lymphocyte count concurrent with recovery from the disease. The counts in the cases with positive cough plates were essentially the same as those

without bacteriologic proof. In adult pertussis, therefore, the blood count is not distinctive enough to be characteristic as is the case in most instances of juvenile pertussis.

CONCLUSION

Adult pertussis occurs more frequently than is generally assumed.

Second attacks are more frequent than is commonly believed.

In adults, pertussis starts with an insidious cough from one to three weeks after exposure. This cough lasts from five to six weeks or longer. It is worse at night and is intensified by such factors as exertion, excitement, eating, and temperature changes. Whooping and vomiting are infrequent, but gagging and choking, common. A thick, white, tenacious phlegm is raised.

Positive cough plates were obtained in six of our cases. The clinical picture and blood studies in these six were similar to the remaining cases.

The blood count in adult pertussis is not as characteristic as in the juvenile cases and usually is of no value in diagnosis.

The rôle of missed cases of pertussis in adults in the epidemiology of the disease is emphasized.

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5502 GROVE STREET

SICKLE-CELL ANEMIA IN A WHITE AMERICAN FAMILY

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SICKLE-CELL anemia is now noted with some frequency in the Negro, and sicklemia, or the tendency for sickled erythrocytes to occur without anemia is recognized in between 5 and 10 per cent of the colored race. Until relatively recently the condition was believed not to occur in other races, but several instances have been reported in the past few years. Cooley and Lee,[1] for example, have observed sickle-cell anemia in a Greek family; Archibald,[2] in an Arab; Stewart,[3] in a Cuban (Spanish); and Rosenfeld and Pineus,[4] in an Italian. Sights and Simon[5] have reported the only instance in a native white American with Scotch-Irish parentage. In this paper we wish to report the instance of a white American family, in which two children suffered from a severe form of sickle-cell anemia and their father had sicklemia. In one child, an infant, one year old, splenectomy was performed without effect on the sickling or on the anemia.

Familial History.—The two children to be reported were the youngest of six children, all living, the others being two sisters, aged nine and eight years, and two brothers, aged seven and five years. These siblings were all examined, and none showed anemia or sickling although each had a palpable spleen. Their father, thirty-six years old, had no anemia, nor was his spleen palpable, but the blood showed typical sickling after from twelve to twenty-four hours. He was an only child, but, by a previous marriage his father had had a daughter, who is still living in Illinois, but was not examined. His parents had died when he was a boy, the father of pneumonia and the mother in childbirth. His maternal grandmother died at the age of eighty. His father's only brother and their father had come from Ohio. Most of the family records had been destroyed by fire, but there was no knowledge of any alien blood. Although the inheritance in the children was obviously from the father, their maternal ancestry was also investigated. The mother, twenty-five years old, was also an only child. She had no anemia or evidence of sickling. Her father was dead, but her mother, forty-five years old, had normal blood, without sickling, and stated that none of her fourteen brothers and sisters nor her husband's family had had any apparent anemia. Her forebears had come from Virginia and Kentucky, and she had no knowledge of any Negro or Mediterranean ancestry.

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From all information obtainable, this is a typical midwestern American family, without suspicion of Negro or Southern European ancestry for four generations. The appearance of the individual members does not suggest alien blood (Figs. 1 and 2). The detailed family history is presented because in the only other case reported[5] in a white American, the familial observations are so meager that the possibility of alien ancestry is hard to exclude, and the phenomenon of sicklemia in the patient, who had syphilis and malaria, was apparently transient and could not be demonstrated on repeated later examinations.

CASE 1.—Richard H., was first seen at the age of ten months with anemia and an enlarged spleen. Pallor, noted when he was two months old, increased until a transfusion was given four months later. Improvement lasted only a few weeks, and a second transfusion was given at nine months of age, with similar temporary benefit. There had been no jaundice or other symptoms except slight weakness and a tendency to vomit his feedings when the anemia became severe. The baby had been breast fed for seven months and since then had been on adequate artificial feeding. Development had been normal except that teething was slightly delayed.

On examination the infant was moderately atonic and undernourished, and weighed 13¾ pounds (6,250 gm.). The only significant physical findings were marked pallor, moderately enlarged liver, and a firm spleen which extended below the umbilicus. The blood showed 28 per cent hemoglobin with slightly more than a million erythrocytes, poikilocytosis, and anisocytosis, some polychromatophilia, and a few normoblasts. The leucocytes appeared normal. Sickling was not noted in stained films, and wet preparations were not examined. Bleeding and clotting time, normal; platelets 155,000; blood group "A"; fragility test—hemolysis began at 0.42 and was complete at 0.32; blood Wassermann negative; serum protein, nonprotein nitrogen, chlorides, and CO_2 content within normal limits; urine, negative; intradermal tuberculin test negative. A roentgenogram of the skull showed two small dark areas suggestive of rarefaction surrounded by a poorly defined zone of increased density in the anterior parietal region adjacent to the midportion of the coronal suture.

Course.—Transfusions brought the blood count to 4,000,000 within a week, but a month later it had fallen to 2,500,000 with a picture of primary anemia similar to that seen on admission. There were moderate variations in the size of the spleen during this time, the organ becoming larger as the anemia increased and regressing somewhat following transfusion. Further transfusions were given, and at the age of twelve and one-half months splenectomy was performed. The color remained good for slightly more than a month, but the anemia returned and, three months after the operation, transfusion was again necessary since the count had fallen to 2,500,000. At this time blood films showed large numbers of normoblasts.

Not until two months after the splenectomy when sickle-cell anemia was diagnosed in the sister (Case 2), was the nature of the condition recognized, and then wet preparations after from twelve to twenty-four hours showed typical sickling. A moist preparation had been examined previously, but no true sickling was seen during an hour or more, there being only a slight distortion of erythrocytes. This slow development of the characteristic changes in the blood cells was constant in the three members of this family with sicklemia.

Fig. 1 shows a photograph of this patient, taken two months after the operation. He is definitely retarded in physical development, but less so than his sister (Case 2).

The spleen removed at operation weighed 112 grams and measured 11 cm. by 8 cm. by 4 cm. We are indebted to Dr. Margaret Smith of the Department of Pathology for the following description: "There are fairly numerous large malpighian bodies with large germinal centers. A few malpighian bodies, however,

Fig. 1.—Patient 1, fifteen months of age, two and one-half months after splenectomy. Height 28.4 in. (71 cm.), weight 14.5 pounds. (6.6 kg.). Average for fifteen months is 30.5 in. (76 cm.) and 22.5 pounds (10.2 kg.).

have been largely replaced by connective tissue. In one or two such areas there is hemorrhage near the small central artery, but not surrounding the fibrotic malpighian body. Sometimes, at the edge of normal malpighian bodies, in the red pulp quite separated from them, are small nodules of large vacuolated, indefinitely outlined cells with elongated vesicular nuclei superficially resembling tubercles composed of epitheloid cells. For the most part the sinuses are flattened and difficult to out-

line. The pulp spaces are packed with red blood cells, most of which have assumed greatly elongated spindle or bizarre forms, the characteristic appearance of the blood cells in tissues of individuals whose red cells have shown sickling during life. The localized hemorrhage about malpighian bodies seen in the spleen of such individuals is absent. There are no deposits of iron pigment or of calcium."

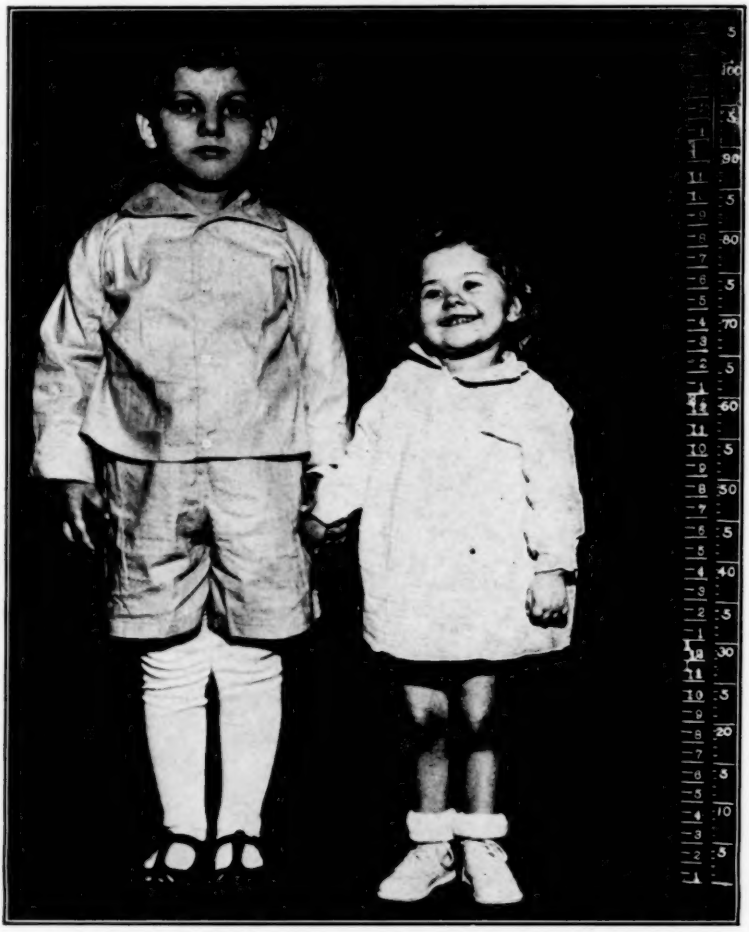

Fig. 2.—Patient 2 (right), three and one-half years of age, height 32 in. (80 cm.), weight 20 pounds (9 kg.), compared with a child of identical age (left) of normal development.

CASE 2.—About six weeks after splenectomy was performed on the first patient, his sister Betty, three and one-half years old, was admitted with fever and drowsiness of three days' duration. She had always been small in stature and pale, and at times had suffered from attacks of fever and headache lasting several days. She had developed normally except for her size, was bright and active, and her diet had been varied and adequate except that she disliked milk.

On examination, although her temperature was 39.8° C. (103.6° F.), she did not appear acutely ill, and the only physical findings of importance concerned her anemia and dwarfing. She was well proportioned and moderately well nourished but weighed only 19 pounds (8.6 kg.) and was but 32 inches (80 cm.) in height. Her photograph, taken a few weeks later beside a normally developed child of identical age is shown in Fig. 2. She had an extreme pallor; the liver was palpable 3 cm. below the costal margin; but the spleen was not felt. The blood showed anemia with a count of 2,500,000, 35 per cent hemoglobin, marked poikilocytosis, anisocytosis, and basophilia. Erythroblasts were present in very large numbers, forming more than 1 per cent of the red cells. It was suggested by Dr. Thomas B. Cooley, to whom a blood film was shown, that such a picture was rare except in sickle-cell anemia, and that this patient might be of the type of "slow sickling,"

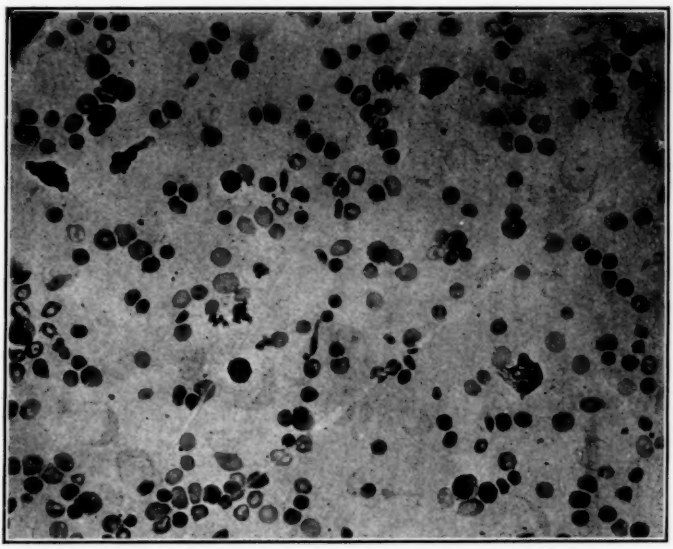

Fig. 3.—Patient 2. Photomicrograph of a fresh, stained blood film (Wright's stain) during severe anemia, and showing numerous normoblasts but no sickling. The crescent-shaped bodies are artefacts.

in which the distortion of the erythrocytes appeared only after a number of hours. Wet preparations made subsequently showed typical sickling after from twelve to twenty-four hours. Photomicrographs of a stained fresh blood film with many nucleated erythrocytes, but no sickling, and of a twenty-four-hour wet preparation illustrating the irregular distorted cells including sickle forms are shown in Figs. 3, 4 and 5.

No other significant abnormalities were found in the blood. Platelets were 230,000; bleeding and clotting time, normal; blood group, "A"; fragility test—hemolysis began at 0.44 and was complete at 0.34; leucocytes, normal; Wassermann, intradermal tuberculin, and urine, negative; blood protein and nonprotein nitrogen, within normal limits. Roentgenograms of skull, upper, and lower extremities, hands, and feet showed no abnormalities except that only two centers of ossification were present for the carpal and tarsal bones on each side.

Fig. 4.

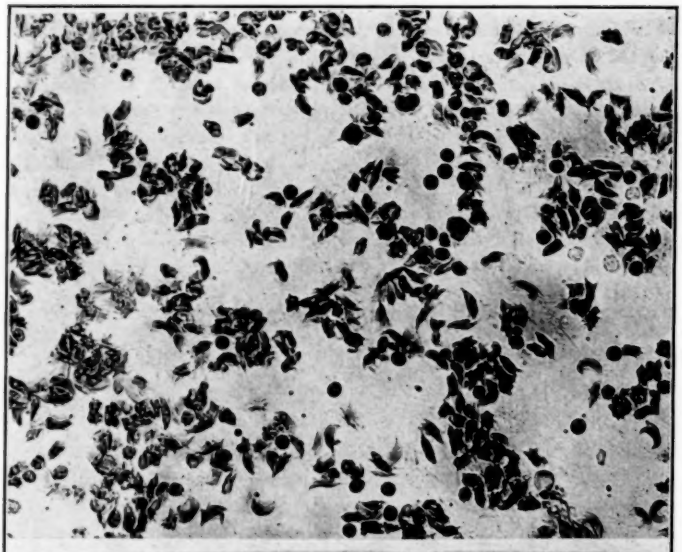

Fig. 5.

Fig. 4.—Patient 2. Photomicrograph of a moist blood film after twenty-four hours, with many sickled erythrocytes. Moderate magnification.

Fig. 5.—Patient 2. Photomicrograph of moist blood film after twenty-four hours, showing crenation, sickling, and other bizarre forms of erythrocytes. High magnification.

Course.—Following several transfusions the temperature fell to normal within a week; the color improved; and the blood became normal except for the slow sickling which could always be demonstrated. From a count of 5 million the erythrocytes fell gradually during the next two months and her spleen became palpable. At

times she has complained of transient pain in the legs but never any abdominal pain. No conclusion was drawn regarding the possible relation of the continued anemia to the dwarfing and delayed epiphyseal bone growth. The child had no other evidence of cretinism.

SUMMARY

In a white American family with no evidence of Negro or Mediterranean ancestry, two children, aged one and three and one-half years, suffered from sickle-cell anemia since early infancy. Their father had sicklemia without anemia. In all the sickling was of the slow type, which requires from twelve to twenty-four hours to appear. Both children were stunted in growth, the girl being more dwarfed than her baby brother. The removal of an enlarged spleen in the younger child failed to affect the anemia or the sickling, while the spleen in the other patient was small. The noteworthy features in these cases, in addition to their ethnologic interest, concerns the early age at which symptoms of anemia appeared in both children and the slow type of sickling. It is suggested that even in anemia of white American children, the possibility of sickle-cell anemia should be remembered and a moist blood film examined after being kept twenty-four hours.

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PRIMARY CARCINOMA OF THE KIDNEY IN CHILDHOOD

Review of Literature; Case Report With Necropsy

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THE carcinoma of the kidney presented in this article has several points of interest: (1) the age of the patient, (2) the paucity and short duration of clinical symptoms, (3) the sudden death, (4) the extensive metastases, (5) the histologic character of the neoplasm.

CASE REPORT

The patient, a boy, eight years old, was admitted to the Pediatric Service of City Hospital, March 13, 1933. Except for measles and diphtheria two years previously, he had always been in good health. One week before entrance to the hospital, the mother had noticed that the child was short of breath and had paroxysmal spells of coughing, occurring chiefly at night and occasionally with blood-streaked sputum. Since the onset of the paroxysms he had been losing weight. The morning of admission, she was taking the child to a clinic for a physical examination when he suddenly had a generalized convulsive seizure and became unconscious. He entered the hospital about twenty minutes later.

He was in coma and extremely dyspneic. The extremities were blue and cold. The pulse was rapid and almost imperceptible. The right chest appeared normal, the left was hyperresonant. A few râles were heard at the angle of the left scapula. The abdomen was tense and of normal size and shape. The organs could not be palpated because of the tense abdominal muscles. Death occurred approximately within five minutes after admission to the ward. The clinical diagnosis was possible spontaneous pneumothorax, probably due to tuberculosis.

Autopsy was performed two and one-half hours later. The pertinent findings only are given.

On opening the abdomen, the right diaphragm presented a nodular convexity bulging downward below the costal margin, displacing the liver, lower border of which reached the iliac crest. The right pleural sac was obliterated, the mesial border of the lung lying to the left of the midline and displacing the heart. The left lung was air-containing and the pleural sac free of gas, fluid, and adhesions. The pericardial sac was normal. When the pulmonary artery was opened, a large, soft, friable, opaque white thrombus was found completely occluding both main branches and extending well into both lungs.

The left kidney weighed 300 gm. The upper pole was nodular. On section, the entire upper half of the kidney was replaced by confluent masses, opaque white in color, mottled with small ochre yellow areas, and reaching the pelvis. The center had the silvery white color of scar tissue. Toward the midportion of the kidney the masses were smaller and directly continuous with the larger masses as prolonga-

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tions through the venous channels, serial cuts revealing the arcuate veins at the midpoint completely thrombosed, with extensions into the adjacent cortex and medulla. All the veins draining the upper two-thirds of the kidney were thrombosed by neoplasm. The main renal vein was greatly distended, the thrombus just projecting as a ragged torn surface into the lumen of the inferior vena cava. The lower pole of the kidney was free of neoplastic masses; its vein was distended by fluid blood.

The left renal lymphatic chain, the peri-aortic glands from the level of the renal arteries to the diaphragm, and the glands at the root of the mesentery were enlarged, hard, and white on section.

The right lung appeared very large and nodular. On section it was completely encased by malignant tissue and firmly adherent to the diaphragm. This malignant

Fig. 1.—Cross-section of the left kidney. Two-thirds of the organ is replaced by confluent tumor masses. The thrombosed renal vein can be seen below the normal lower pole.

shell was nodular, firm and white with ochre yellow mottling in some portions. Over the lower half of the lung the masses were very large and had numerous large cysts, some containing amber-colored or hemorrhagic fluid. The inner wall of some of the cysts was smooth; others had hard cauliflower masses projecting into the cavity. The parenchyma of the lung was very slightly involved in the subpleural region around blood vessels.

On the pleural surface of the left lower lobe were some small, white spiderlike placques with white prolongations extending into the parenchyma.

The superior tracheobronchial lymph nodes of both sides were normal. The inferior tracheobronchial nodes were extremely large, hard, and opaque white on the cut surface; the central node was about the size of a hen's egg. On the right,

the pleuropulmonary nodes were similar but smaller. On the left, there was still less involvement.

The other organs were entirely normal.

Histology.—The tissues were fixed in 10 per cent formalin, and stained by the following methods: hematoxylin and eosin, Van Gieson, Mallory's connective tissue, Weigert's elastic tissue, Maresh-Bielschowsky, sudan III. About twenty-five blocks from various portions of the kidney were examined.

Left Kidney: The chief characteristic of the tumor was the papillary formation. The cells were high cuboidal or columnar, and the cell membranes were frequently curiously well defined. The cells were of two types. One, greatly predominant in numbers, had an opaque, finely granular cytoplasm. The other, much fewer in number, was interspersed among the opaque cells. Its cytoplasm was

Fig. 2.—Coronal section of the thoracic organs. The main pulmonary arteries are occluded by the neoplastic embolus. The right lung is completely encased by neoplasm. Cyst formation is particularly prominent over the lower lobe. Just above the pulmonary arteries is the very large inferior tracheobronchial lymph node completely replaced by malignancy.

clear and had masses of fine golden brown threads. These cells were in sharp contrast to the opaque cells. The nuclei of the cells of both types varied somewhat in size and shape, had a tendency to hyperchromatism; some were in mitosis. Fat deposit within the cells was extremely scanty and limited to a very few foci. The epithelium rested directly upon a capillary vessel; a distinct basal membrane could not be demonstrated. In the upper pole, in the region appearing grossly similar to scar tissue, was a moderate desmoplastic reaction. There was no sarcomatous element; the connective tissue was dense, acellular and hyaline. The neoplasm extended through the veins and capillaries, compressing the parenchyma. A heavy lymphoid reaction was present at the periphery. The lower pole was perfectly normal.

Fig. 3.

Fig. 4.

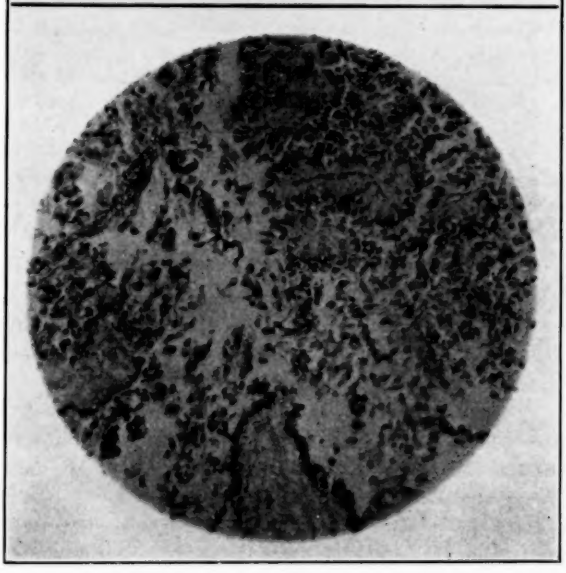

Fig. 3.—Photomicrograph of the carcinoma of the kidney, showing the typical papillary formation.

Fig. 4.—Photomicrograph through the wall of a small cyst in right pleura. The papillary formation is well developed. On one side can be seen the type of desmoid reaction.

The thrombus of the renal veins presented the same papillary formation. The opaque cell only was present. The central core of the papillae was denser than in the main tumor, and its connective tissue was invaded by small nests and individual neoplastic cells.

Aortic and Renal Lymph Nodes: The normal structure was completely replaced by the papillary neoplasm. The desmoplastic reaction was much more marked than in the original mass.

Right Lung: The most striking feature of the pleural involvement was the papillary formation, duplicating that seen in the kidney. In some places a distinct basement membrane could be demonstrated. As a rule the connective tissue core was more prominent. It consisted of normal connective tissue enclosing a thin-walled capillary; neoplastic cells were not found invading the core. The walls of the macroscopic cysts were lined by from low cuboidal to high columnar cells; some had small papillary excrescences. Some of the very small cysts had thick hyaline connective tissue walls containing phagocytic cells filled with hemosiderin. The small cysts were filled with masses of anaplastic cells. The extension into the lung parenchyma was along the periarterial and peribronchial lymph channels and was quite limited, corresponding closely to the gross appearance of freedom of the parenchyma.

Left Lung: The small spiderlike placques of the pleural surface had the same general papillary type of growth.

Bronchial Lymph Nodes: All the features seen in the pleura were present with the exception of the cyst formation. The desmoplastic reaction was especially intense.

Main Pulmonary Arteries: The main feature of the embolus was the marked papillary formation. Desmoplastic reaction was absent.

Anatomical Diagnoses: Primary papillary adenocarcinoma of the left kidney; metastases to draining lymph nodes, pleura, and bronchial lymph nodes; carcinomatous thrombosis of left renal vein; carcinomatous embolus of main pulmonary arteries.

Dr. Douglas Symmers and Dr. Martha Wollstein kindly reviewed the sections and examined the gross specimen and agreed with the diagnosis. They both stated that they had never seen any structure resembling this case in any Wilms tumors.

In childhood the kidney is a favorite site of primary malignant neoplasms. D'Espine and Piso[1] rank it second only to the eye and orbit. Steffen,[2] in a much larger series, ranks the kidney and suprarenal as a more frequent site. Mixter[3] states that the kidney is certainly the most frequent site and places its incidence at from 20 to 25 per cent of all malignancies occurring in the first decade. The greatest portion of the neoplasms, however, are sarcomatous in nature. Ewing[4] states that the carcinomas are rare in comparison to the mixed tumors. Schultz[5] expresses the opinion that probably all cases reported as carcinoma are mixed tumors. Mixter likewise is doubtful of the occurrence of true epithelial growths in children and remarks that if further study could be made of the rare cases so diagnosed among the kidney tumors seen in the Children's Hospital of Boston, reclassification as Wilms tumors would probably be necessary.

Of 1,063 carcinomas of the kidney studied by Gallard,[6] only six occurred in the first decade. Porter and Carter[7] found, in a period of

five years, three carcinomas in nine neoplasms of the kidney in children; all the children were less than seven years of age. Albarran and Imbert,[8] in a study of 170 epithelial tumors, had seven carcinomas and two adenocarcinomas.

The hypernephroma is even rarer than the carcinoma. Schmieden[9] reported one involving the left kidney in a three-year-old child. Frank's[10] case involved the right kidney in a child, eight and one-half years old. The case of Warner[11] was in a two-year-old girl.

The cases of carcinoma of the kidney have many features in common. In Bokai's[12] case, a boy of five and one-half years, a left-sided abdominal mass had been present for one year. The child, however, did not appear ill, and had no pain; hematuria had never been noticed. He was emaciated and anemic. The mass filled more than half of the abdomen and grew rapidly. On removal, the neoplasm weighed 4 kg. Death occurred three days postoperatively. The histologic diagnosis was medullary carcinoma. At autopsy no metastases were found.

A five-year-old girl seen by Barth[13] had a mass in the right flank, which had first been noticed by the mother one month previously. Hematuria had occurred once. The mass grew rapidly, and the child lost weight. Nephrectomy was performed successfully, the child being discharged after a stormy convalescence. The subsequent history is not stated. The histologic diagnosis was adenocarcinoma.

The case of Ilott and Walsham,[14] a nine-and-one-half-month-old male, had a mass in the left abdomen of one month's duration. There had occurred some bronchial attacks, occasional pain and difficulty of urination, and hematuria on one occasion. Nephrectomy was performed. Convalescence was stormy. The pathologic diagnosis was congenital cystic adenoma, glandular in type, without any tendency to papillary formation. The histology led to the hope that a cure had been attained. Seven months later, the child was still well but within the next four months, a rapidly growing tumor recurred at the original site.

In Malcolm's case,[15] a boy twenty-three months old, it was noticed that at the age of one year "it had a full belly," but a definite mass in the right side was not noticed until six months later. When first seen by Malcolm, the infant was in good health. The tumor filled the entire right groin and reached the midline. The urine was normal. Nephrectomy was performed, a draining lymph node also being removed. The histologic diagnosis was malignant adenoma; it was noted that no sarcomatous element was present, and the lymph node was free of metastases. Three years later the child was well and free from any demonstrable metastases.

Perthes[16] had three cases. His first case, in a girl four and one-half years old, had a mass of three months' duration filling the entire left half of the abdomen. It consisted of two portions, one the size of a child's head, the other the size of a fist. The pathologic diagnosis was

adenocarcinoma. Eleven months after nephrectomy, death occurred from basilar meningitis, no evidence of recurrence having presented.

His second case presented several unusual features. For four years, a mass in the right side was known to have been present in this patient, a boy, nine years of age. The pathologic report of the kidney removed was adenocarcinoma. Death occurred five years later, probably from metastases.

In another nine-year-old boy, Perthes found a mass filling the left hypochondrium, reaching halfway from umbilicus to symphysis, and passing a hand's breadth beyond the midline. It had first been noticed two months previously and was accompanied by pain. At operation, the tumor proved difficult to remove because of friability and hemorrhage. Death occurred two days after operation. The pathologic diagnosis was carcinoma.

Phelip and Salin[17] report a rapidly growing tumor of the left hypochondrium of one month's duration in a girl twenty-one months old. Loss of weight had occurred but no other symptoms were present. The tumor was easily removed and was diagnosed histologically as carcinoma.

The patient of Dies[18] was a four-year-old girl. For three months the abdomen had been increasing in size and becoming hard from a right-sided mass. Loss of weight had occurred only recently. The urine was normal. Nephrectomy was followed by a postoperative death in a few hours. The pathologic diagnosis was adenocarcinoma.

The five-year-old girl seen by Simone[19] had the remarkably short history of illness of one week. The mother had noticed that the child was feverish and had an enlarged abdomen. The tumor mass filled the entire right half of the abdomen and flank. The urine was negative. Aspiration revealed neoplastic cells. A postoperative death followed nephrectomy. The pathologic diagnosis was papillary adenocarcinoma.

DISCUSSION

The presenting symptom in the majority of the cases has been tumor. This feature is similar to the sarcomas of the kidney of the same age period. Wide variations in size, however, occur, from the small bilateral tumors in the case of Weigert[20] to the thirty-one-pound one of the left kidney in an eight-year-old mentioned by Morris.[21]

Hematuria, in contrast to the neoplasms of the adult and similar to the sarcomas of children, is an infrequent symptom. Many textbooks on pediatrics state that this symptom is frequent but it is now being recognized that hematuria in kidney neoplasms in childhood is infrequent and quite in contrast to its prominence in the adult. In two cases only was it mentioned. In Barth's case, it was noted once; in that of Ilott and Walsham, occasionally.

When the cases first came under observation, it was usually noted that the general health was good. Loss of weight, when present, had occurred only recently.

There appears to be no special period of the first decade more liable to the development of carcinoma. Weigert's case was a stillbirth with bilateral small carcinomas. In the first year are two cases, those of Ilott and Walsham and of Manasse[22]; in the second year, two, Malcolm, and Phelip and Salin; in the fourth, two, Perthes and Dies; in the fifth, three, Bokai, Barth, and Simone; in the eighth, one, Morris; in the ninth, two, both of Perthes. Gallard's six cases and the one of Lubarsch[23] were all less than ten years of age; those of Porter and Carter, less than seven. Albarran and Imbert list their cases simply as occurring in childhood. Kaufmann[24] saw one case in a child twelve years of age.

Neither kidney seems more susceptible, nor does sex appear to play any rôle.

The duration of the disease was usually one year or less. The second case of Perthes is most unusual in its extremely long duration of nine years. Postoperative death occurred in four of ten cases. There was one three-year cure and one case with metastases occurring after five years.

Metastases are stated by Bokai to be infrequent. In the case of Ilott and Walsham and one of Perthes, recurrences appeared. Our own case presented unusually widespread metastases. The secondary deposits in the tracheobronchial nodes unquestionably gave rise to the presenting symptoms, the primary site being entirely silent.

The histology of all the cases has been characterized by the resemblance to renal tubules. Many cases have had cyst formation. A very few have had papillary formation as a striking feature. In only one, the unusual case of Weigert, were there structures resembling imperfect glomeruli. In our own case, the most striking feature was the papillary formation. In the pleural metastases, cyst formation, entirely absent at the original site, was very marked. Other regions of the pleura were medullary and anaplastic. The desmoplastic reaction in pleura and bronchial lymph nodes was extreme.

SUMMARY

The clinical features of the cases of carcinoma of the kidney in childhood bear a striking resemblance to those of sarcoma. It is a disease of signs rather than symptoms. The presenting sign is usually the enlarging abdomen, leading to the discovery of a tumor mass. Hematuria is rare. Pain occurs seldom and is more likely to be a sense of discomfort from the presence of a large mass. The general symptoms of anemia and emaciation occur late in the course and are frequently absent when the case first comes under observation. The only therapy

offering any hope of cure is nephrectomy. Prognosis must be guarded as the postoperative death rate is high. The tendency for metastases to be absent or late in the large majority of cases, however, leads to the hope that earlier diagnosis may improve the prognosis.

CONCLUSIONS

The literature of carcinoma of the kidney in childhood is reviewed and a case is reported.

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ACUTE INFECTIOUS CROUP

A General Study of Acute Obstructive Infections of the Larynx, Trachea, and Bronchi With an Analysis of 727 Cases

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PART II. ACUTE NONSPECIFIC INFECTIOUS CROUP

This condition is called by a number of names, such as acute catarrhal croup, acute laryngitis, acute laryngotracheobronchitis, acute nondiphtheritic croup, acute obstructive nondiphtheritic laryngitis, streptococcic laryngotracheitis, septic laryngitis, and so on. As was pointed out at the beginning of this paper, an etiologic rather than a pathologic nomenclature is desirable. Moreover, each of these terms lacks uniform significance. For example, the diagnosis, "acute catarrhal laryngitis," given as the cause of death by one man, may imply to another merely slight hoarseness due to overuse of the voice. We, therefore, propose to use the term "acute nonspecific infectious croup" to denote an acute obstructive inflammation of the larynx, alone or together with the trachea and bronchi, associated with certain pyogenic organisms, particularly streptococci and staphylococci. In describing each case, we give the etiology and the extent of the involvement whenever possible.

LIVING PATHOLOGY

The same factors that contribute to the local pathologic changes of diphtheritic croup—edema, exudate, membrane, and spasm—are also present here, differing only in frequency of occurrence and in degree.

Edema.—There may be an angry red, boggy swelling of the epiglottis, the aryepiglottic folds, and the false cords preventing complete visualization of the glottis. This may be so great as to distort these structures beyond recognition. In other cases, the congestion and swelling are limited to the subglottic region. But, most characteristically there is involvement to a varying degree of the regions above and below the vocal cords.

Exudation.—This varies in amount and character with the severity of the infection. In mild cases, it may be scanty or absent entirely, mucoid or mucopurulent. In severe cases with involvement of the

trachea, bronchi, and bronchioles, exudation is always profuse, usually thick and tenacious and sometimes so ropy that it cannot be expectorated. If it is not removed, it becomes gummy, often hindering the separation of the vocal cords and plugging the subglottic region; then, it becomes dry, hard, and brittle so as to resemble a foreign body and to act as one.

Membrane.—In a few very virulent infections from which only streptococci were recovered, definite membrane was found in the larynx and trachea. This was thin and white and could not be distinguished grossly from the membrane in an early case of diphtheria. When the patient was observed for several days, it was found that the consistency of the membrane being produced remained unchanged, differing in this respect from diphtheritic membrane, which becomes thicker, firmer, and less friable as the disease progresses. In one patient, who recovered from a severe laryngotracheobronchitis and septicemia caused by a hemolytic streptococcus, thick fibrinous membrane, similar to that in late diphtheria, was removed by suction from the trachea and bronchi through a tracheotomy tube. In another, who gave a history of diphtheria immunization and a negative Schick test, thick, well-formed membrane was aspirated from the larynx, trachea, and right bronchus; and repeated cultures from the nose, throat, and larynx showed only a *Streptococcus hemolyticus*. The child required intubation for seven days and made an uneventful recovery.

CLASSIFICATION

The disease can be subdivided anatomically as follows:

I. Acute nonspecific infectious laryngitis
II. Acute nonspecific infectious laryngotracheitis
III. Acute nonspecific infectious laryngotracheobronchitis with or without septicemia

It must be admitted that this classification is arbitrary to some extent because it is often difficult to place a case in any one of these categories. However, certain gross characteristics distinguish each of these groups, and such an anatomic grouping is valuable from the standpoint of therapy, prognosis, and as a basis for comparing results of different workers.

Group I. Acute Nonspecific Infectious Laryngitis

There is usually a moderate amount of congestion and edema above the vocal cords and less than moderate subglottic swelling. The exudate is thin and scanty. Hoarseness is usually slight, but at times there may be marked aphonia. Respiratory embarrassment is generally slight or moderate.

Uncommonly there may be considerable swelling and congestion of the epiglottis, the aryepiglottic folds, and arytenoids so that the glottis is obscured. This swelling may be so extreme that the entire region is distorted beyond recognition, and the glottis cannot be seen at all. In these cases respiratory difficulty is severe and the type of breathing is unique. There is a characteristic, low-pitched, coarse, inspiratory stridor, and a longer and louder, expiratory rattle. This is so typical that it has enabled us to recognize the presence of extreme supraglottic edema before laryngoscopy. Furthermore, the practiced finger can readily feel the supraglottic swelling, and thus the diagnosis can be confirmed without laryngoscopy.

Group II. Acute Nonspecific Infectious Laryngotracheitis

In addition to what has been described as the usual picture of laryngitis, there is present enough subglottic edema to narrow the lumen to less than half its normal size, sometimes, to a barely visible chink. The inflammation is not limited to the subglottic region but involves the tracheal mucosa as well, as is evidenced by the increased secretion and by postmortem findings. There is usually found a moderate or a considerable amount of mucopurulent exudate, which may be thin or thick, gummy, solidified, or pseudomembranous. These patients have more than moderate, often extremely severe, respiratory difficulty and cause us grave concern. Many of them, no doubt, have some degree of bronchial involvement. However, they have not been placed in Group III, because they do not show clinical evidence of bronchial obstruction by profuse secretion.

Group III. Acute Nonspecific Infectious Laryngotracheobronchitis

This is characterized by a profuse outpouring of ropy, gummy, inspissated, or pseudomembranous bronchial exudate, which causes frequently repeated obstruction requiring relief. Bronchopneumonia is an almost constant complication, and septicemia is a frequent finding. Fever is high; respiration, rapid; and the patients look toxemic and prostrated.

INCIDENCE

Frequency.—Of the 727 cases of croup studied 400, or 55 per cent, fell into this nonspecific group. Of these, 294 had laryngeal involvement; eighty-four, laryngotracheal; and twenty-two, laryngotracheobronchial involvement.

Seasonal.—The disease was endemic the year round with a low ebb in June, July, and August. Each subgroup followed this general fre-

quency curve, tending to show that they are cases of different severity of the same disease rather than distinct entities, as has been suggested by some.

Age.—The youngest patient was three months old, the oldest fifty years. Eleven were over fourteen years, as follows: 16, 19, 20, 20, 21, 24, 30, 38, 40, 47, and 50 years old; 11.7 per cent of the patients were less than one year old; 46 per cent were in the second and third years of life; 78 per cent were under five; 16.5 per cent were from five to nine years old; and 5.5 per cent over nine.

Under 6 months	5 cases
6 to 12 months	42 cases
1 to 2 years	116 cases
2 to 3 years	69 cases
3 to 4 years	52 cases
4 to 5 years	28 cases
5 to 6 years	22 cases
6 to 7 years	17 cases
7 to 8 years	16 cases
8 to 9 years	11 cases
9 to 10 years	3 cases
10 to 11 years	3 cases
11 to 12 years	3 cases
12 to 13 years	2 cases
14 and over	11 cases

Sex.—There were 287 males, or 72 per cent, and 113 females, or 28 per cent.

DIAGNOSIS

Onset.—The onset of this type of croup is usually more sudden and catastrophic than that of diphtheritic croup. Thus, a child previously well, often with no prodromes except a slight cough and some fever, may within a few hours develop extreme respiratory distress. However, many patients have a more gradual onset similar to that in diphtheria. The following is a list of symptoms that were found on the first day of illness:

Cough	51 per cent of cases
Dyspnea	45 per cent of cases
Hoarseness	32 per cent of cases
Fever	23 per cent of cases
Rhinitis	20 per cent of cases
Angina	17 per cent of cases

Thus, an irritative cough occurs on the first day of illness in half the cases and is closely followed in frequency by dyspnea and less

often by hoarseness. In the individual patient, too, these symptoms usually appear in the same chronologic order—cough, dyspnea, and hoarseness. This difference from the sequence in diphtheria, namely, cough, hoarseness and then dyspnea, can be explained by the difference in the character and spread of the underlying pathologic changes. In these nonspecific infections edema above and below the vocal cords is the chief offending factor, and, until the cords become greatly congested and covered with exudate or are encroached upon by the edema, the voice remains quite clear or only slightly hoarse, even while the patient is quite dyspneic.

SYMPTOMATOLOGY

Local Symptoms.—Hoarseness: As just discussed, hoarseness is usually not as prominent as in diphtheritic laryngitis, and the cough is more phonic, barking, and less constricted. However, in some cases of severe dyspnea with sticky, mucopurulent exudate, the voice may be lost completely, and the cough may become short and toneless as in diphtheria.

Dyspnea: The dyspnea does not usually grow progressively more severe as in diphtheria. Many patients have definite remissions of one day or more during which there may be no respiratory difficulty whatsoever. In such patients, as well as in those without remissions, stertor and dyspnea usually become worse at night. Once developed, the dyspnea, clinically, looks exactly like that due to diphtheria.

General Symptoms.—Fever: The temperature is usually higher than in diphtheritic croup. However, the average admission temperature was only 101.2° F. This low average, similar to that in diphtheria, was evidently due to the larger number of mild cases. In confirmation of this is the fact that 29 per cent of these patients had a temperature of 103° F. or more as compared with only 14 per cent in the diphtheritic group. The age did not seem to affect the temperature, but the subgrouping revealed striking contrasts. Thus, in Group I sixty-seven of the patients, or 23 per cent, had a temperature of 103° F. or more; in Group II, twenty-four, or 28 per cent; and in Group III, twenty, or 91 per cent.

Leucocytosis: The white blood cell counts varied considerably. The average was 11,600 with 69 per cent polymorphonuclear cells. No definite relationship could be found between the count and the age of the patient or the day of illness on which the count was taken. The number of white cells was generally proportionate to the percentage of polymorphonuclear cells and to the height of the temperature.

Pulse: Excepting the very severe cases, the pulse was accelerated even less than the expected ten beats per degree rise of temperature

above normal. In patients with severe dyspnea and septicemia, the pulse became rapid, out of proportion to the fever, thready and impalpable. As in diphtheria, with severe dyspnea there was an "aspiration" pulse.

General Reaction to Local Obstruction: Patients with severe respiratory obstruction develop the same general reactions to this obstruction as described above under diphtheria.

Bacteriology.—A single culture swab, applied directly to the larynx during laryngoscopy, was implanted upon two Löffler slants, one chocolate agar slant and one tube of culture broth. One of the Löffler slants was sent to the laboratory of the New York City Department of Health to rule out diphtheria. The three other cultures were sent to the laboratory of the Willard Parker Hospital to be examined for predominating organisms. From the latter, reports were obtained in 254 cases as follows:

Streptococcus hemolyticus in pure culture	72 cases (28%)
Streptococcus viridans in pure culture	45 cases (18%)
Staphylococcus aureus in pure culture	13 cases (5%)
Bacillus influenzae in pure culture	3 cases (1%)
Some kind of streptococcus, alone or combined with other organisms, was found in	234 cases (92%)
Streptococcus hemolyticus alone or in combination occurred in	177 cases (70%)
Streptococcus viridans alone or in combination occurred in	130 cases (51%)
Staphylococcus aureus alone or in combination occurred in	71 cases (28%)

The following list gives the frequency of the various combinations

Streptococcus hemolyticus and *viridans*	54 cases
Streptococcus hemolyticus and *Staphylococcus aureus*	29 cases
Streptococcus hemolyticus and *Bacillus influenzae*	2 cases
Streptococcus hemolyticus and *viridans* with *Staphylococcus aureus*	11 cases
Streptococcus hemolyticus and *viridans* with *Bacillus influenzae*	2 cases
Streptococcus hemolyticus and *viridans* with *Micrococcus catarrhalis*	2 cases
Streptococcus hemolyticus and *viridans* with *Bacillus hoffmanni*	1 case
Streptococcus hemolyticus and *viridans* with *Bacillus pyocyaneus*	1 case
Streptococcus hemolyticus and *Staphylococcus aureus* with *Bacillus influenzae*	1 case
Streptococcus hemolyticus and *Staphylococcus aureus*, *Streptococcus viridans* and *Micrococcus catarrhalis*	1 case
Streptococcus hemolyticus and *viridans*, *Staphylococcus aureus*, *Bacillus influenzae*, *Micrococcus catarrhalis*	1 case
Streptococcus viridans and *Staphylococcus aureus*	9 cases

Streptococcus viridans, Staphylococcus aureus and *Micrococcus catarrhalis*	1 case
Streptococcus viridans and *Staphylococcus aureus* with *Bacillus influenzae*	1 case
Streptococcus viridans, Bacillus pyocyaneus and *Micrococcus catarrhalis*	1 case
Staphylococcus aureus with *Bacillus influenzae*	3 cases
Staphylococcus aureus and *Bacillus pyocyaneus* with *Micrococcus catarrhalis*	1 case

Klebs-Löffler bacilli were reported in twenty (8 per cent) of the cases cited above. These patients showed no clinical evidence of diphtheria, had negative Schick tests, and recovered without diphtheria antitoxin. These were evidently incidental findings not unusual in a group of this kind.

The authors were unable to draw any definite conclusions as to the relative virulences of the different organisms as shown by the extent of involvement of the respiratory tract, the duration of illness, the treatment required, the complications developed, and the mortality. None of the patients showing the *B. influenzae*, the *B. pyocyaneus*, or the *M. catarrhalis* died or displayed any unusual features. Every patient who was intubated or tracheotomized had either *Streptococcus hemolyticus* or *Streptococcus viridans* or both, alone or combined with other organisms.

TREATMENT

Most of the patients suffering from acute nonspecific infectious croup recover with palliative treatment alone. However, in the others some type of mechanical intervention becomes absolutely necessary as a life-saving measure.

In *simple laryngitis* the treatment is rest in bed, a tepid soapsuds enema, steam inhalations, ipecac, whisky, phenobarbital, a liquid diet, and plenty of fluids. If coughing is excessive, small doses of codeine may be given. Mechanical intervention is not required and should be avoided. Only when the laryngitis is complicated by extreme supraglottic edema causing severe respiratory embarrassment is mechanical intervention indicated.

In cases of acute *laryngotracheitis*, which are characterized by obstructive subglottic edema and increased secretion, in addition to the above treatment, we give ice caps, alcohol sponges, cool enemata, and antipyretics in order to reduce high fever, thus lowering the metabolic rate and consequently the oxygen requirement. In more severe cases we also administer oxygen by nasal catheter or place the patient in an oxygen tent to tide him over the acute stage for from twelve to twenty-four hours, when the edema usually begins to subside. However, a small percentage of these patients have such extreme subglottic

edema and obstructing secretion that all these measures are ineffective and mechanical intervention is imperative.

In acute *laryngotracheobronchitis*, which is characterized by extreme subglottic swelling associated with profuse secretions poured out from the entire extent of the tracheobronchial tree, all palliative measures are of no avail, and mechanical intervention must be resorted to. Moreover, since these cases are usually complicated by bronchopneumonia and often by septicemia, even these measures, aided by infusions and transfusions, too often fail to save the life of the patient.

The general indications for mechanical intervention and the means at our disposal in these cases are exactly identical with those in diphtheritic croup, which are given in Part I. Indications for selecting each special type of intervention are as follows:

A. *Suction:* When the obstruction is caused by tenacious, ropy, gummy, inspissated or membranous secretions.

B. *Intubation:* Some writers believe that intubation is definitely contraindicated in nondiphtheritic croup and, therefore, perform tracheotomies. However, we feel that when the obstruction is due mainly to subglottic edema, intubation is helpful and far less dangerous than routine tracheotomy. We agree with Baum,[23] who feels that the dry, cool air inhaled through the tracheotomy tube predisposes to the formation of gummy, dried crusts in the bronchi and may thus lead to a fatal outcome. Whenever possible, he prefers intubation to tracheotomy. Richards,[24] on the other hand, disapproves of intubation because the child coughs when taking food and for that reason refuses all fluids. This can be easily remedied by gavage which we employ routinely and have found satisfactory.

C. *Suction-Intubation:* When suction alone gives inadequate relief due to the subglottic swelling and intubation alone gives only moderate relief due to the obstruction by secretions, the combined suction-intubation treatment is used.

D. *Tracheotomy:* 1. When there is extreme subglottic edema requiring intubation, together with profuse, ropy secretions, which cause repeated blocking of the tube and repeated asphyxial attacks with the likelihood of cardiac exhaustion, tracheotomy should not be postponed too long.

2. As in diphtheria, when the tube is coughed up too frequently and results in too rapid an onset of severe dyspnea, a tracheotomy should be performed to avoid the danger of death from asphyxia or exhaustion. Richards[24] says, "Two or more replacements (due to cough-up) will almost certainly necessitate a tracheotomy before extubation may be successfully accomplished." Our experience has not substantiated this opinion.

3. When the tube is found to be ineffective because of supraglottic edema overlapping it above or subtubal edema blocking it below, tracheotomy must be performed. However, we have never encountered a case in which edema below the tube caused enough obstruction to require tracheotomy.

4. When there is extreme supraglottic edema, which the experienced operator can see will not be benefited and may even be made worse by intubation, a tracheotomy should be performed at once without wasting valuable time doing a trial intubation. The latter may give some relief but may also irritate the inflamed supraglottic tissues, causing an increase in the edema. This may cause an overlapping of the tube and may result in sudden asphyxia (due to the indrawing of the overlapping tissues on inspiration) necessitating an immediate, urgent tracheotomy. It is preferable to anticipate such an event by performing an elective tracheotomy early. Should such an accident occur, a long metal tube should be inserted into the trachea to provide a certain airway while the tracheotomy is being performed. For this purpose Mosher's life-saving tube, a Willard Parker suction tube, or a bronchoscope may be used.

5. When there is danger of the patient becoming a chronic tube carrier, tracheotomy is performed, just as in diphtheria.

A low tracheotomy is done by making a simple, linear incision through the third, fourth, and fifth rings. Sutures are better dispensed with since they have a tendency to cause pocketing of air and usually slough away in three or four days, anyway.

The more important part of tracheotomy is the after-care, which consists of measures to prevent blocking of the tracheotomy tube, the trachea, and the bronchi. Following operation, the patient is placed in a cubicle, which has a canvas covering on the top and on the one open side, and steam is supplied from a large electric kettle. The foot of the bed is raised in order to provide postural drainage. The tube is covered with several loose layers of gauze kept moist with warm boric acid solution. Several drops of warm, 5 per cent solution of sodium bicarbonate are dropped into the tracheotomy tube every ten or fifteen minutes for the first day, then less often, as necessary. Tracheal suction with a soft rubber catheter is performed every quarter or half-hour for the first two days, then when indicated. Since these children are unable to develop a good cough because of the tracheotomy opening, we plug the tube with the finger during several successive expirations every hour or two. This causes a good caughing spell and thus helps dislodge secretions in the smaller bronchi. A high fluid intake is essential. If enough is not taken by mouth, gavage and clyses are used. For high fevers, alcohol sponges, ice caps, cool en-

emas, and antipyretics are given. Sedatives are indicated, but they should not be too strong.

Specially trained nurses on duty every minute are essential for good results. They should be given careful, minute instructions in every case and be told to call the doctor *at once* when any perplexing situation arises.

In one case, a nurse did not call the doctor until after five minutes of dyspnea, cyanosis, and restlessness. She said she had found the tracheotomy tube patent on repeated suction. The tube had been dislodged from the trachea and was lying alongside it within the wound. This could not be detected from external appearances. Fortunately, delay in this instance did not result fatally because a partial airway remained. Nurses are instructed to place the tips of the fingers over the tracheotomy tube to test for volume and force of the air blast. If these are diminished and cannot be remedied by suction, they are told to inform the doctor in charge at once.

To remove plugs of mucopus in the bronchi, we never employ bronchoscopes or forceps in the manner recommended by Lyman Richards.[24] We obtain satisfactory results by using rubber catheters, Willard Parker suction tubes, or bronchoscopic suction tubes. In no case did clinical or postmortem examination reveal the presence of gummy or inspissated material after our method of suction. When pushing the rubber catheter through the tracheotomy tube, it should be timed with inspiration, and the suction should be cut off; otherwise the tip will stick to the tracheal or bronchial wall, making its insertion impossible. In a few instances, we have to resort to the metal tubes which are inserted through the tracheotomy wound or the larynx, depending on the case.

Illustrative Cases

Case Tided Over Without Intervention.—A three-year-old boy, son of a physician, was sent in on the third day of illness. He had been seen by throat specialists, who advised intubation or tracheotomy. The child was acutely ill, nearly aphonic, pale, slightly cyanotic, with deep retractions, and considerable suppression of breath sounds throughout the chest. His temperature was 103° F., pulse 140, and respiration 34. Laryngoscopy showed congestion and moderate supraglottic edema. The cords could barely be seen. There was no exudate or membrane, but there was a great deal of subglottic edema which was causing the dyspnea. During laryngoscopy the dyspnea became more severe, the retractions deeper, and the cyanosis more intense, so that it seemed that an intubation would surely have to be performed. However, the child was put to bed, given a cool colonic irrigation, an alcohol sponge, an ice cap, and oxygen by nasal catheter. For the next thirty-six hours, during which he had attacks of dyspnea and restlessness, he was carefully watched and disturbed as little as possible. He recovered without any complications and was discharged on the eleventh day of illness. On follow-up a year later, he showed normal laryngeal function and was in fine health.

Cases to Illustrate the Suction Treatment.—One Suction: A ten-month-old baby girl was admitted on the second day of illness, acutely ill, pale, moderately cyanotic, with loud respiratory stridor, deep retractions, and absent breath sounds. Laryngoscopy showed considerable congestion, some edema above the cords, and stringy, sticky, grayish exudate between and below the cords, completely blocking the lumen. Suction removed this and gave immediate, complete relief. There was moderate subglottic edema. She was given the usual palliative treatment and was discharged five days later completely cured. Cultures from the larynx showed *Streptococcus viridans.*

Two Suctions: A four-month-old infant girl was admitted on the fourth day of illness with a temperature of 103.8° F.; pulse was 170, and respirations, 60. She was acutely ill, nearly aphonic, pale and moderately cyanotic, severely dyspneic, with deep retractions, and absent breath sounds. Expiration was more difficult than inspiration. Laryngoscopy showed congestion and moderate edema above the cords and more than moderate subglottic edema. Suction below the cords removed some fibrinopurulent exudate and gave a moderate amount of relief. The child was given palliative treatment and oxygen by nasal catheter. A roentgen-ray examination taken a few hours after admission showed evidence of pneumonia in the right paravertebral region. During the next two days the patient had a moderate degree of dyspnea, then the temperature rose to 105.2° F., and the dyspnea became more severe; the retractions, deeper. Laryngoscopy showed considerable supraglottic edema and extreme subglottic edema, but no membrane or exudate. The open suction tube was inserted, without suction being applied, and held in the subglottic region for five seconds. The area was swabbed with adrenalin solution (1:1,000). Breathing became a good deal easier. This was done in order to avoid intubation. A prolonged alcohol sponge was given taking the temperature down to 102° F. The child's condition improved remarkably. At this time there was evidence of bronchopneumonia in the left lower lobe and right upper lobe. During the next two days the temperature ranged between 100.4° F. and 102° F., and there was only mild respiratory obstruction. Then the temperature rose to 105° F.; pulse, 170; respirations, 60; retractions became deeper; and cyanosis appeared. Because of the obstruction, a laryngoscopy was done. This showed a more than moderate supraglottic and subglottic edema and thick, tenacious mucopus plugging the lumen. Suction removed this and gave complete relief. The fever fell precipitously to 100° F. in two hours, and there were no signs of obstruction to breathing during the rest of the illness. The bronchopneumonia cleared up gradually, and the child was discharged on the twenty-seventh day of illness. Cultures from the larynx showed *Streptococcus viridans.* On follow-up one year later, the patient was found to be normal in every way.

Case to Illustrate Intubation.—A three-year-old female child was admitted on the second day of illness. She was acutely ill, moderately cyanotic, severely dyspneic with deep retractions and absent breath sounds. Laryngoscopy showed moderate supraglottic congestion and edema and extreme subglottic edema. No exudate or membrane was seen. Her condition required immediate intubation. This was done. The child was completely relieved at once and fell into a deep sleep while still on the table. Five days later she was extubated on trial, but after sixteen hours the dyspnea became quite severe. On laryngoscopy she was found to have considerable subglottic edema, but no exudate or membrane. She was reintubated and completely relieved. Four days later, another trial extubation was successful, and the child was discharged completely cured on the eighteenth day of illness. Cultures from the larynx showed *Streptococcus viridans.*

Case to Illustrate Suction and Intubation.—An eight-month-old baby girl was admitted on the fifth day of illness acutely ill, with slight hoarseness, moderate dyspnea and retractions, and slightly suppressed breath sounds. A diagnostic laryngoscopy showed moderate supraglottic and subglottic edema and a moderate amount of mucopus. A culture was taken, but no suction was applied. The child continued to be moderately dyspneic for two days. Then retractions became deeper; respirations, more rapid; and breath sounds, more distant. A laryngoscopy showed extreme subglottic edema and a moderate amount of mucopurulent exudate. Aspiration gave only slight relief, and the child had to be intubated with a size six-month tube, which gave complete relief. After thirty-six hours dyspnea became severe, and laryngoscopy showed the tube to be blocked with stringy mucopus. The tube was removed, and suction was applied to the larynx and trachea. This did not give sufficient relief so that a size six-month tube was inserted, and the child fell asleep at once. Two and a half days later the tube was coughed up but had to be replaced in an hour and a half. Two days later it was again coughed up, and the child became extremely dyspneic. Laryngoscopy showed extreme subglottic edema and tenacious mucopus clogging the lumen. This was removed, and the child was greatly relieved. However, ten minutes later obstructive symptoms increased to such an extent that the tube had to be replaced. Six hours after this the tube was again coughed up, but this time did not have to be replaced. The child was discharged completely cured on the twenty-fourth day of illness. Cultures from the larynx showed *Streptococcus viridans.*

Case With Frequent Cough-Up of Tube in Which Tracheotomy Was Avoided.—A two-year-old baby girl was admitted on the second day of illness acutely and desperately ill, with severe retractions, complete suppression of breath sounds, moderate pallor, and cyanosis. Laryngoscopy showed moderate supraglottic and extreme subglottic edema and a moderate amount of stringy mucopus. This was removed by suction, which gave only temporary relief; she was intubated with a size nine-month tube, the one-year size proving to be too large. She was completely relieved within a minute. The tube was coughed up at intervals of twelve, sixteen, twenty-five, and eight hours and had to be replaced within from one-half to six hours after each cough-up. Six hours later, it was again coughed up and had to be put back two hours after that, this time a size one-year tube being used. Five days later, a trial extubation was performed, but within a half hour the dyspnea became so great that she had to be reintubated with a size nine-month tube. Three hours later she again became very dyspneic. Laryngoscopy showed the tube to be blocked with mucopus. It was removed, and the larynx and trachea were given a suction treatment. Two and a half hours later she had to be reintubated with a size one-year tube. Within the next nine hours, the tube became blocked twice and had to be removed and replaced. Four days later the tube was coughed up and did not have to be put back. Nine days later, the voice was strong, clear, and of normal pitch. During her illness she developed a moderate degree of atelectasis of the right upper lobe, which cleared up while in the hospital. The child was discharged cured on the thirty-first day of illness. A year later she was in perfect health and had a strong clear voice of normal pitch. There had been no recurrences of croup.

1. *Tracheotomy Necessitated by Blocking by Secretions:* There were five patients in whom tracheotomy had to be performed because of repeated blocking of the intubation tube. All five died. The following case is typical.

A nine-month-old infant was admitted on the seventh day of an illness characterized by cough, hoarseness, and dyspnea which had become progressively worse. On

admission he was moderately dyspneic; color was good; and lungs, clear. A diagnostic laryngoscopy revealed moderate supraglottic edema and congestion and considerable subglottic edema and mucopurulent exudate. Two hours later the dyspnea and restlessness increased, and laryngoscopy showed increased subglottic edema. A size six-month tube was inserted, and the patient was completely relieved at once. However, seven hours later it was coughed up and had to be replaced within an hour. After fourteen hours, the infant became very dyspneic, restless, and cyanotic; laryngoscopy showed the tube blocked with sticky mucopus. The tube was changed, and the child, completely relieved. Since this blocking recurred twice in the next four hours, a tracheotomy was performed. At this time the temperature rose to 105.6° F.; there were scattered râles throughout the chest. The tracheotomy relieved the respiratory distress, but the child's general condition remained very poor. The day after the operation he developed convulsive twitchings of the arms and legs. He was given a transfusion of 100 c.c. of whole blood, but he did not improve and died four days after admission. Roentgen-ray examination had suggested the presence of bronchopneumonia in the right and left upper lobes and an interlobar pleurisy between the right upper and right middle lobes. A blood culture during life showed a *Streptococcus hemolyticus*. Postmortem examination showed early bronchopneumonia in the right upper, the right lower, and the left upper lobes. The smaller bronchi were filled with a mucopurulent material. Many petechial hemorrhages were seen on the surface of the lungs. Two small pus cavities and interstitial emphysema were found in the mediastinum. The larynx, trachea, and bronchi were markedly injected. Cultures of the heart's blood, from the trachea, mediastinum, and lungs all showed a *Streptococcus hemolyticus*.

2. *Tracheotomy Necessitated by Cough-Up:* There were three patients who required a tracheotomy because of repeated cough-up of the intubation tube. All three recovered. This illustrative case is cited.

A fifteen-month-old baby girl was admitted on the first day of illness with severe respiratory difficulty, deep retractions, very distant breath sounds, and moderate pallor. Laryngoscopy showed extreme subglottic edema, slight supraglottic edema, and a slight amount of thin exudate. Cultures were taken, and the child was put to bed and given palliative treatment. After two hours, her condition becoming much worse, she was intubated with a size nine-month tube and was completely relieved. Twenty-three hours later the child became very dyspneic and had deep retractions. Laryngoscopy confirmed the suspicion that the tube had been coughed up and probably swallowed. She was reintubated with a size nine-month tube but coughed it up nine hours later and was again reintubated, this time with a size one-year tube. Four days later a trial extubation was unsuccessful, the tube having to be replaced within a few minutes because of the extreme dyspnea. In the next six days the tube was coughed up seven times and had to be replaced each time. Because of this, tracheotomy was done. Three days later she developed a partial collapse of the right upper lobe; this cleared up in three days. Sixteen days after the operation the tracheotomy tube was removed, and the child was discharged cured on the thirty-ninth day of illness. Cultures from the larynx showed *Streptococcus hemolyticus* and *viridans*. On follow-up a year later, the child was found to be in good health, with a clear, strong voice, but of somewhat lower pitch than normal. She had had three mild attacks of croup lasting one night each since her discharge from the hospital.

3. *Tracheotomy in a Case of Supraglottic Edema With Intubation:* In two patients trial intubation was ineffective and was followed by tracheotomy. Both recovered. The case report of one of these is given for illustration.

A two-year-old male child, when admitted on the seventh day of illness, was acutely and desperately ill, exhausted, extremely pale and moderately cyanotic, with severe respiratory distress, and moderate suprasternal and substernal retractions. His eyes were sunken; he was dehydrated. Breath sounds were greatly suppressed all over. Laryngoscopy showed extreme edema and congestion of the supraglottic structures so that the glottis could not be seen. No exudate or membrane was visible. A size two-year tube gave no relief; therefore, a size three-year tube was inserted allowing it to project slightly above the edematous tissues. This gave a moderate degree of relief. As preparations for tracheotomy were being made, the child was taken to the operating room. When he was placed on the table, he suddenly collapsed, stopped breathing, became ashy white, unconscious; generalized convulsions followed. A tracheotomy was quickly performed and artificial respiration given. This revived the child, but the heart action was extremely poor and the pulse barely perceptible. The child improved gradually, and the tracheotomy tube was removed fifteen days later. He was discharged cured on the thirty-first day of illness.

4. *Tracheotomy in a Case of Supraglottic Edema Without Intubation:* Eight patients required emergency trancheotomies because of extreme supraglottic edema. Three of these recovered. The following case is an illustration.

A two-year-old boy was admitted on the second day of illness, acutely and desperately ill, with the type of breathing peculiar to patients with extreme supraglottic edema, namely, a loud inspiratory stridor and a much louder rattling expiratory stridor. The voice was practically normal. There were deep suprasternal retractions but only mild substernal retractions. Breath sounds were entirely masked by stridor. The uvula was extremely congested and swollen, the tip being covered with membrane. The other parts of the throat were very red, but clear. The diagnosis of extreme supraglottic edema, suspected because of the peculiar breathing, was confirmed by laryngoscopy, which showed distortion and edema of the supraglottic structures preventing visualization of the glottis. A tracheotomy soon performed gave complete relief. The next day the child developed a moderate degree of subcutaneous emphysema around the neck. Three days later thick pieces of membrane looking exactly like that found in diphtheria were removed by suction from the trachea and bronchi through the tracheotomy tube. At this time physical signs suggested fluid in the right side of the chest. By thoracentesis 25 c.c. of thin, cloudy, amber-colored fluid were obtained. Pure cultures of a hemolytic streptococcus were obtained from the blood stream on admission, from the fluid in the pleural cavity, from the larynx and trachea, and from the membrane removed. Five days after admission both middle ears became infected, and the same organism was grown from the purulent discharge. The edema of the larynx subsided gradually, and the tracheotomy tube was removed seven days after the operation. The patient was discharged completely cured on the thirty-fourth day of illness.

5. *Tracheotomy Necessitated by "Chronic Tube":* There were no such cases in our series.

COMPLICATIONS OF NONSPECIFIC CROUP

Classification of Complications

I. Following closely upon local obstruction
- A. Pneumonia
  - 1. Bronchopneumonia
  - 2. Lobar pneumonia
- B. Atelectasis
  - 1. Patchy
  - 2. Lobar
- C. Emphysema
  - 1. Pulmonary
  - 2. Extrapulmonary
    - a. Subcutaneous
    - b. Mediastinal
- D. Pneumothorax
- E. Myocardial failure

II. Due to superimposed secondary infections
- A. Empyema—pleurisy
- B. Septicemia
- C. Myocarditis, pericarditis, endocarditis
- D. Mediastinitis
- E. Thymitis
- F. Appendicitis
- G. Otitis media
- H. Pyelitis
- I. Arthritis
- J. Noma
- K. Erysipelas
- L. Cellulitis

Order of Frequency of Complications

Otitis media	27 cases	7 per cent
Pneumonia	21 cases	5 per cent
Atelectasis	13 cases	3 per cent
Myocarditis	12 cases	3 per cent
Septicemia	11 cases	3 per cent
Mediastinitis	5 cases	
Empyema	4 cases	
Pleurisy	3 cases	
Pneumothorax	3 cases	
Appendicitis, thymitis and pericarditis	2 cases each	
Endocarditis, cellulitis and erysipelas of the neck, noma, pyelitis	1 case each	

The total number of patients suffering from complications was sixty-one, or 15 per cent.

Pneumonia.—Pneumonia occurred in 5 per cent of the nonspecific croups. Its incidence did not seem to be affected by the season of the year or the age of the patient. The anatomic group into which the case fell was the most important factor in predisposing to pneumonia.

Group I: 6 pneumonia cases in 294 patients, or 2 per cent
Group II: 7 pneumonia cases in 84 patients, or 8 per cent
Group III: 8 pneumonia cases in 22 patients, or 36 per cent

Bacteriology: Laryngeal cultures obtained in nineteen of the patients who developed pneumonia were as follows:

Streptococcus hemolyticus	4 cases
Streptococcus hemolyticus and *Staphylococcus aureus*	5 cases
Streptococcus hemolyticus and *Bacillus influenzae*	1 case
Streptococcus hemolyticus and *Streptococcus viridans*	2 cases
Streptococcus hemolyticus, Streptococcus viridans, and *Staphylococcus aureus*	2 cases
Streptococcus hemolyticus and *Micrococcus catarrhalis*	1 case
Streptococcus hemolyticus, Micrococcus catarrhalis, Staphylococcus aureus, and *Bacillus influenzae*	1 case
Streptococcus viridans	2 cases
Streptococcus viridans and *Staphylococcus aureus*	1 case

Postmortem cultures obtained from the lungs were almost uniformly a hemolytic streptococcus.

Correlation of the incidence of pneumonia with mechanical treatment required showed:

Patients receiving no mechanical treatment	8 out of 332 cases, or 2 per cent
Patients receiving suction	4 out of 29 cases, or 14 per cent
Patients receiving suction-intubation	5 out of 21 cases, or 24 per cent
Patients receiving tracheotomy	5 out of 18 cases, or 28 per cent

As discussed under diphtheria, the development of pneumonia cannot be ascribed to the type of treatment given since the case with more extensive involvement required more radical intervention. As in diphtheria, pneumonia set in early in the disease, almost always within the first week. The disease was bronchopneumonic in all cases but sometimes became almost lobar in extent due to the confluence of patches of peribronchial lesions. The right lung was invaded in all but five cases. The right upper lobe was involved in thirteen cases; the right middle lobe, in four. In no case was the right lower lobe alone involved. In eight cases the disease became fairly widespread, extending to several lobes. The illness was long drawn out in all cases. The roentgen-ray findings remained positive for from two weeks to two months.

Mortality: Eight of the pneumonic patients died, a mortality of 38 per cent. All but one of these were in Group III.

Atelectasis.—Atelectasis, which occurred in thirteen cases, was usually of the same type and distribution as in diphtheritic croup and just as free from clinical features. The complication occurred always before

the fifth day of illness; it was of short duration, usually under a week, and bore the following relationship to the mechanical treatment required:

Patients receiving no mechanical treatment,	6 cases
Patients receiving suction,	1 case
Patients receiving suction-intubation,	5 cases
Patients receiving tracheotomy,	1 case

Lobar collapse occurred in two cases, in both instances involving the right upper lobe. One patient received suction and intubation; the other required no mechanical intervention. The collapse persisted for several weeks.

Emphysema.—Pulmonary emphysema was found occasionally on necropsy. It never constituted a conspicuous part of the clinical picture. Gross subcutaneous or mediastinal emphysema did not occur except in conjunction with tracheotomy.

Pneumothorax.—Pneumothorax occurred in three cases in conjunction with tracheotomy. We do not believe that the mediastinum or the pleural spaces were opened into at the time of operation. Instead, the air was probably sucked into the wound and passed alongside the trachea into the mediastinum, later rupturing through the pleura to cause the pneumothorax. All these patients had subcutaneous and mediastinal emphysema. This pathway is the reverse of that which the air usually takes in leaving the alveolar spaces and appearing in the mediastinum or subcutaneous tissues. The occurrence of such emphysema following tracheotomy is believed to be due to the fact that the disease was so extensive, down to the periphery of the bronchioles, that the obstruction was only partially relieved by the operation. As a result, the retractions continued and led to the sucking in of air through the wound with each inspiration and its expression into the tissue spaces with each expiration.[25]

The first patient developed a 20 per cent right pneumothorax, which was noticed three days after the tracheotomy. Three days later, the lung was almost completely reexpanded. The patient recovered. The second patient developed a 50 per cent left pneumothorax, which was noticed ten hours after the tracheotomy. The patient died ten hours later. The third patient developed a 75 per cent bilateral pneumothorax, which was noticed three hours after the tracheotomy. The patient died the same day. The two patients who died showed severe symptoms coincident with the onset of the pneumothorax. Both had frequent blocking of the tracheotomy tube and required repeated suction of the trachea and bronchi.

Myocardial Failure.—Clinical evidences of myocardial failure existed in twelve cases; associated with sepsis in six; mediastinitis in three;

pneumonia, empyema, and pericarditis in two; and pyelitis, appendicitis, endocarditis, cellulitis, erysipelas, acute rheumatic fever, and thymitis in one each. All but two died. The complication bore the following relationship to the treatment required:

Patients requiring no mechanical treatment,	3 cases
Patients requiring suction,	no case
Patients requiring intubation,	2 cases
Patients requiring tracheotomy,	7 cases

Secondary Infections

Empyema occurred in four cases. In one patient who was tracheotomized because of extreme supraglottic edema, there was an associated septicemia and bilateral otitis media. This patient had laryngotracheobronchitis. Cultures from the larynx, ears, chest fluid, and blood showed a hemolytic streptococcus. The patient recovered. Another child was tracheotomized because of extreme supraglottic edema. After two days the tracheotomy tube was removed, and the wound was closed. Roentgen-ray examination showed fluid in the left pleural cavity and pointed to probable pericardial effusion. About 5 c.c. of very thick pus was aspirated from the chest. The child died in a few days; postmortem examination revealed about 400 c.c. of thick, custardlike material in the pericardial and pleural cavities. The pleura was almost 2 cm. thick. The *B. influenzae* was recovered from both the pleural and pericardial fluids. A third child required suction and intubation and developed bilateral otitis media, left-sided bronchopneumonia, and empyema. The child recovered after thoracotomy. The fourth child required suction and intubation and developed an interlobal empyema between the right upper and middle lobes. This cleared up, and the child recovered.

Septicemia occurred in eleven patients, seven of whom died. It was associated with myocarditis in six; pneumonia and mediastinitis in three; appendicitis and empyema in two; and cellulitis, erysipelas, pericarditis, pyelitis, arthritis, and noma in one each. One patient had septicemia and no other complication. Four of the patients had extreme supraglottic edema as a prominent feature of the disease.

Bacteriology: In three patients, *Streptococcus viridans* was obtained from both blood and larynx. Two of these died. In four patients, *Streptococcus hemolyticus* was obtained from both blood and larynx. All died. One patient, who showed *Streptococcus hemolyticus* in the blood, larynx and trachea, ears and chest fluid, recovered. One patient, who showed a hemolytic streptococcus in the blood and *Streptococcus viridans* in the larynx, died. Another patient, who showed a gram-positive diplococcus in the blood and a hemolytic streptococcus in the

bronchi, also died. One patient, who had Pneumococcus Type XXII (Bullowa-Cooper) in the blood and *Streptococcus hemolyticus, Streptococcus viridans,* and *Staphylococcus aureus* in the larynx, recovered. Furthermore, postmortem blood cultures were obtained in four cases in which none were obtained during life. One showed a hemolytic streptococcus in the heart, wrist joint, and a gland; another, in the heart alone. In a third both *Streptococcus hemolyticus* and *Staphylococcus aureus* were cultured from the heart's blood. The fourth had *Streptococcus hemolyticus* and *viridans* in the heart, larynx, and bronchi.

Otitis media occurred in twenty-seven patients, none of whom died.

Mediastinitis.—This occurred in five cases and was diagnosed at necropsy.

Appendicitis.—In two fulminating septicemic cases, appendicitis was found on necropsy. In both instances the diagnosis was not made during life.

Fulminating Laryngotracheobronchitis and Appendicitis in Streptococcus Septicemia.—A three-year-old boy was admitted with a history of hoarseness and dyspnea of four hours' duration. On admission he looked acutely ill, had deep suprasternal and substernal retractions, and greatly diminished breath sounds throughout the entire chest. A laryngoscopy showed considerable congestion and edema of the supraglottic structures and moderate subglottic edema. The temperature was 102° F.; the pulse, 140; respirations, 32. He was put to bed for observation, but fifteen minutes later, without any warning he suddenly stopped breathing. He was immediately intubated and given artificial respiration but did not revive. One of the authors was greatly upset over the cause of this sudden and unexpected death until the postmortem examination was made. This showed vegetations of recent origin on the mitral and tricuspid valves and extreme engorgement of the pericardial vessels. The cellular tissues of the mediastinum were involved in a process of gelatinous edema formation. The thymus was extremely congested. There was boggy edema of the epiglottis and larynx and necrosis of the mucosa of the ventricles, trachea, and bronchi. The appendix was long and tortuous, and its distal extremity contained about a dram of thick, creamy yellow pus. Cultures from the larynx, bronchi, appendix, and the heart's blood showed *Streptococcus hemolyticus* and *viridans.* This was apparently a blood-borne, fulminating case of streptococcic laryngotracheobronchitis, which developed endocarditis, appendicitis, and mediastinitis.

Laryngotracheitis and Appendicitis in Streptococcus Septicemia.—A thirty-year-old man was sent in from another hospital with a diagnosis of diphtheritic croup. He had been given 20,000 units of diphtheria antitoxin. His illness began one week before with a cold, followed in two days by hoarseness, aphonia, and stridor, and later by abdominal pain, hiccough, and vomiting. For the preceding two days, he had had increasing difficulty in breathing. On admission he was acutely ill and slightly cyanotic. Breathing was stertorous and labored with overaction of the accessory muscles of respiration and moderate retractions. The breath sounds were greatly suppressed throughout. The heart sounds were of fairly good quality, rapid, and regular. He hiccoughed frequently; he did not complain of abdominal pain; and there was no tenderness. Direct laryngoscopy showed extreme congestion, edema and deformity of the supraglottic structures so that the glottis was partially obscured. No exudate or membrane was seen. He was put to bed for observation.

During the next eighteen hours his breathing was easier; then he became more dyspneic, restless, and moderately cyanotic. A direct laryngoscopy revealed extreme supraglottic edema so that the glottis could not be visualized. While this was being done, he stopped breathing but was revived by artificial respiration. A tracheotomy was performed at once and gave complete respiratory relief. At this time the heart beat was irregular, with frequent dropped beats, and the sounds were of poor quality. He was given intravenous glucose and was digitalized. The next day his breathing was easy; his general condition appeared better, but the heart sounds were of poor quality. The systolic pressure was 78; the diastolic, 64. The temperature was 104° F. His heart action continued to grow weaker, and he died the following day. Admission cultures from the throat, the larynx, and the blood showed *Streptococcus hemolyticus.*

Postmortem examination revealed the following:

The myocardium showed widespread, patchy sclerosis and a high degree of coronary sclerosis. The pleura was studded with petechial hemorrhages. The lungs were deeply congested, and there were areas suggesting early bronchopneumonia. The mediastinal tissues were very edematous and emphysematous. The larynx and trachea were extremely swollen and inflamed. An abscess was found in the intercostal muscle between the second and third ribs on the left side, and the large bulbous appendix, when opened, was found to be distended with creamy yellow pus. Cultures of the heart's blood, appendix, and intercostal abscess all showed *Streptococcus hemolyticus.*

There were two cases of pericarditis. Endocarditis, cellulitis, erysipelas, noma, thymitis, and pyelitis each occurred once in the series.

PROGNOSIS

Age.—There was no definite relationship between the age groups and the duration of illness or the incidence of complications, nor was there any striking correlation between age and mortality rate. There was only one death out of forty-seven patients under one year of age. Two adults, aged thirty and forty-seven years, died. The remaining sixteen deaths occurred among 265 patients from one to five years of age. There were no deaths among eighty-three patients between five and thirty years of age.

Season bore no relationship to the duration of illness or to the mortality rate.

Admission blood counts bore no relationship to the duration of illness or to the mortality rate.

Admission temperature bore no relationship to the duration of illness but showed a definite association with the occurrence of specific complications. Otitis media occurred in 5.4 per cent of the patients with temperatures under 102° F. and in 10.1 per cent of those above 102° F.; pneumonia, in 2.7 per cent of those below and in 11.8 per cent of those above 102° F. Furthermore, the height of the admission temperature bore a definite relationship to the total mortality. Below 102° F. there was only one death, or 1 per cent mortality; above 102° F., a 10 per

cent mortality; 105° F. or over, there were three cases with two deaths.

Bacteriology.—It is impossible to draw conclusions prognostically from the types of organisms found on laryngeal culture.

Pathology.—See Table II for results.

RESULTS

Before presenting our results we feel it necessary to point out a few fallacies into which one might be led when drawing conclusions from this type of statistics. In the first place, only the most severe cases were considered for intubation in our series. No patient was intubated unnecessarily. Many patients were sent into the hospital by private doctors and from other hospitals with urgent requests for immediate intubation. In nearly every case we were able to tide them over the acute stage without resorting to intubation. Several patients, who had already been intubated, were extubated upon or within a few hours after admission to the hospital. Patients receiving these unnecessary intubations invariably did well and are not included as intubation cases in our results. Furthermore, comparisons are often wrongly made between different types of cases requiring different types of treatment. Moreover, in comparing similar types of cases the number is often so small that variations in age, duration of illness, the presence of pneumonia, septicemia or other complications make deductions dangerous. Lastly, one cannot compare the mortality rates of cases receiving different types of treatment in order to judge which is the better method since the mortality is lowest in the mildest cases which do not require any mechanical intervention. Not only that, but even comparisons of results in cases given the same type of treatment by different workers is unfair since the indications for instituting the different type of intervention vary too widely. Thus Thenebe[26] reporting fifty-one cases of acute nondiphtheritic laryngeal obstruction stated: "Twenty-three cases were not intubated; there was no mortality. Four cases were intubated without a tracheotomy; one died—mortality, 25 per cent. Twenty-one cases were intubated and tracheotomized; five of these cases died—mortality, 23.8 per cent. Three cases were tracheotomized without intubation; one of these cases died—mortality, 33 per cent. Total mortality of the entire group of cases was 13.7 per cent. Total mortality of the intubated and tracheotomized patients was 25 per cent." Out of fifty-one cases he intubated twenty-five, whereas out of 400 cases we intubated only thirty-one. Out of fifty-one cases he tracheotomized twenty-four, whereas out of 400 cases, we tracheotomized only eighteen, 48 per cent as contrasted to 4.5 per cent. It is obvious that a comparison of tracheotomy results is impossible since only the worst cases were tracheotomized by us. We quote him further in support of this, "Unquestionably it would

not have been necessary to have intubated or tracheotomized some of the cases, but the margin of safety seems so small in the case where intervention is necessary over the case where no intervention is necessary that one fears the consequences of waiting too long." This statement is entirely true, and a comparison of our statistics will give some idea as to how many anxious watchful hours night and day were spent at the bedside judging this margin of safety and not intervening.

As an example of extremely poor judgment and unnecessary intervention, the following case is cited:

A seven-month-old infant was sent in to us from one of the large city hospitals with a diagnosis of possible diphtheritic croup. Its illness began with vomiting soon followed by convulsions and dyspnea. A few hours later when the infant was brought to the other hospital, the obstruction to breathing was so great that the doctor intubated the baby at once. This, he said, gave immediate relief. On admission to our hospital he was breathing very easily, but from the type of breathing we thought the tube was not in the larynx. On being disturbed, the child cried out in a clear voice, thus confirming our suspicions that the tube was in the esophagus. We proceeded to remove the tube by pulling on the string, which had been left attached. However, there seemed to be obstruction, so that we thought it might have been caught in the nasopharynx. Palpation, however, showed it to be in the esophagus. After making the child gag several times, we finally pulled out the tube and to our consternation found it to be as large as those used for children from seven to ten years of age. This tube could never have been inserted into the infant's larynx, and the reader can draw his own conclusions as to the severity of the respiratory obstruction, which was completely relieved by passage into the esophagus of a tube so large that it could by itself cause obstruction by pressure upon the larynx.

All the patients who required only the suction treatment recovered; twenty-four received suction once; five, twice, an average of 1.2 suctions. Of the intubated patients who recovered without tracheotomy, three had one intubation, three had two; four had three; two had four; one had six; and one had ten intubations, an average of 3.2 intubations. Of the four intubated patients who recovered after tracheotomy, one was intubated once; one, four times; one, eleven times; and the fourth, twelve times. The time the intubation tube was in the larynx ranged from three hours to fifteen days, with an average of 5.3 days, in patients who recovered without tracheotomy. The age of the intubated patients who recovered ranged from seven months to seven years. In patients who lived, the tracheotomy tube was removed in from eight to ninety-three days following operation. The average was twenty-seven days. In the three patients who recovered following emergency tracheotomy, without preliminary intubation, because of extreme supraglottic edema, decannulization was successful after an average period of sixteen days. On the other hand, in the three patients who were intubated because of extreme subglottic edema and, after an average period of six days, required tracheotomy

because of too frequent cough-up of the tube, decannulization could not be successfully performed before an average period of fifty days. It is probable that besides the presence of the intubation tube the structural differences of the regions involved contributed to this delay in decannulization.

TABLE II

RESULTS IN ACUTE NONSPECIFIC INFECTIOUS CROUP

TYPE OF CASE	TOTAL	LARYNGITIS	LARYNGOTRACHEITIS	LARYNGOTRACHEOBRONCHITIS
Number of Cases	400	294	84	22
Cases With Extreme Supraglottic Edema	14	3	6	5
Cases Given Palliative Treatment Only	332	291	40	1
Cases Requiring Any Type of Mechanical Treatment	68 (17%)	3	44	21
Cases Requiring Suction Alone	29 (7.3%)	3	26	0
Cases Receiving Suction and Intubation	21 (5.3%)	0	11	10
Cases Treated by Tracheotomy alone	8 (5 died)	0	3 (1 died)	5 (4 died)
Cases Treated by Suction, Intubation and Tracheotomy	10 (5 died)	0	4	6 (5 died)
Total Number of Cases Tracheotomized	18 (4.5%)	0	7	11
Deaths in Cases With Palliative Treatment	2	1	0	1
Deaths in Cases With Suction Treatment	0	0	0	0
Deaths in Cases Requiring Suction and Intubation	7 (33%)	0	2 (18%)	5 (50%)
Deaths in Cases Tracheotomized	10 (56%)	0	1 (14%)	9 (82%)
Total Deaths and Per Cent Mortality	19 (4.8%)	1 (0.3%)	3 (3.6%)	15 (68%)

Discussion of Deaths.—The causes of death given below are based upon the clinical findings and also upon postmortem examination of 60 per cent of the nineteen fatal cases. A single death in Group I was that of a mongolian idiot who died suddenly, for no obvious reason and without respiratory difficulty. Necropsy was not performed.

Of the three deaths in Group II, one was a mongolian idiot who was intubated, developed pneumonia, and died suddenly and unexpectedly. The second child on admission was desperately ill, septic looking, with a temperature of 105.4° F. He required immediate intubation but died within six hours. No necropsies were performed. The third child, tracheotomized because of extreme supraglottic edema, was successfully decannulized after two days, but succumbed to an extensive, influenzal, suppurative pericarditis and empyema three days later.

There were fifteen deaths in Group III. Eight had septicemia, associated with myocarditis in two; myocarditis and pneumonia in a

third; pneumonia in a fourth; noma and suppurative arthritis in a fifth; pyelitis, suppurative appendicitis, pericarditis, vegetative endocarditis, suppurative mediastinitis, and mesenteric lymphadenitis in a sixth; pneumonia, myocarditis, suppurative appendicitis, mediastinitis, and intercostal abscess in a seventh; and cellulitis and erysipelas of the neck, mediastinitis, empyema, pericarditis, myocarditis, and coronary sclerosis in the eighth. The first three and the last two required tracheotomy. Four patients had pneumonia with thick, tenacious, mucopurulent bronchial exudate, which caused repeated blocking and required frequent removal. Three of these were tracheotomized. One patient had extensive intrathoracic infections including pneumonia, myocarditis, thymitis, and suppurative mediastinitis. In the next two patients, unfortunate accidents occurred. One was the case referred to before in which there was laceration of the larynx during intubation. This child had a complete cleft palate and showed a purulent bronchiolitis on necropsy. The other patient had been tracheotomized because of frequent blocking and cough-up of the intubation tube. During the next eight months he continued to produce mucopurulent exudate which collected in the larynx and trachea and could not be expectorated through the glottis. For this reason, he could not go along for more than two or three hours without the tracheotomy tube and required tracheal suction several times a day. One night, without giving his usual warning signs of cough, stertor, and restlessness, he was found dead by the nurse, the tracheotomy tube blocked by secretions.

FOLLOW-UP

Seventeen of the most severe cases were seen within a year after discharge. Three had received only the suction treatment; one patient, once and two, twice. The child who had had one suction had been aphonic throughout his illness and still showed slight hoarseness when crying. Otherwise, all were in good health and had strong, clear voices of normal pitch. There were nine patients who had received suction from one to ten times and intubation from one to ten times, the combined treatment lasting from one to fourteen days. Three patients had received suction, intubation, and tracheotomy. The tracheotomy had been performed after one suction and four, eleven, and twelve intubations, respectively, the combined treatment lasting from three to fourteen days. One patient had been intubated and tracheotomized outside the hospital and another had been tracheotomized by us because of extreme supraglottic edema. All children were in fine health and had strong, clear voices. One child, who had been intubated twelve times and then tracheotomized because of repeated cough-up, was slightly hoarse when crying. Another child, who had been intubated eleven times and then tracheotomized because of repeated

cough-up, had a voice of somewhat lower pitch than normal and gave a history of three mild attacks of croup lasting one night each. In all the other patients the voice was of normal pitch. Two other children gave a history of one mild recurrent attack of croup.

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FOOT OF EAST FIFTEENTH STREET, NEW YORK CITY
FLUSHING, NEW YORK

DIPHTHERITIC MYOCARDITIS

A Review of 496 Cases

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MYOCARDITIS is one of the common complications of diphtheria. It is also the most frequent cause of death in those cases in which toxemia is pronounced. Seldom is it encountered, however, among patients in whom the membrane is limited to the larynx or trachea. In the latter locations mechanical obstruction to respiration is the principal factor endangering life.

Because of the importance of diphtheritic myocarditis we determined to make a study of all diphtheria cases under treatment in the Municipal Contagious Disease Hospital during the five-year period from 1928 to 1932 in which a diagnosis of myocarditis was definitely established.

During the quinquennium referred to, there were 4,671 diphtheria admissions, and among these there were 548 deaths, a case fatality rate of 11 per cent. Myocarditis was definitely demonstrated as a complication in 496 instances or 10.6 per cent of all cases. It is this latter group we have undertaken to analyze.

Table I

Incidence and Mortality of Diphtheria and Diphtheritic Myocarditis

	1928	1929	1930	1931	1932	TOTAL
Total cases of diphtheria	1009	1414	1227	741	280	4671
Total deaths from diphtheria	163	159	144	65	18	548
Diphtheria mortality rate	16%	11%	11.7%	8.7%	6.4%	11.6%
DIPHTHERITIC MYOCARDITIS						
Cases of diphtheritic myocarditis	130	148	134	60	24	496
Deaths from myocarditis	82	84	99	33	10	308
Mortality rate from myocarditis	63%	57%	74%	55%	42%	62% (Aver.)

In Table I is shown the diphtheria admissions by years, the number suffering from myocarditis, and the case fatality rate for those who had this complication. It will be noted that the death rate for those with myocarditis varied from 42 per cent to 74 per cent and that the

From Municipal Contagious Disease Hospital, Chicago Board of Health.
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average was 62 per cent for the five-year period. If the cases in Table I identified as having myocarditis are classified as types of malignant diphtheria they are comparable with Hottinger's[1] report of similar types in Dusseldorf where the mortality rate was 52 per cent for the year 1930.

Little difference was noted in the frequency with which myocarditis occurred in the sexes, there having been 250 males and 246 females. On the other hand, contrary to the experience of some observers, the fatality rate was higher among the males being 67 per cent as compared to 55 per cent for the females. One of us[2] has previously called attention to the fact that the colored race is apparently less susceptible to diphtheria than the white, and we find this view upheld among the 496 myocarditis cases of which but 28, or 5 per cent, were of the colored race.

TABLE II

AGE INCIDENCE OF DIPHTHERITIC MYOCARDITIS

AGE	CASES	PERCENTAGE	DEATHS	MORTALITY RATE
1-5 yr.	201	40	152	75%
6-10 yr.	191	39	103	54%
11-15 yr.	66	13	33	50%
Over 15 yr.	37	8	16	43%

In Table II the cases are divided according to age groups, and, as might be expected, the highest mortality rate occurred in those who were under five years of age. Frequency and case mortality were next greatest in the second five-year period of life while those more than fifteen years of age showed the lowest death rate.

TABLE III

DISTRIBUTION OF MEMBRANE IN 472 CASES OF DIPHTHERITIC MYOCARDITIS

	TOTAL	RECOVERED	DIED	MORTALITY RATE
Tonsillar	39	35	4	11%
Tonsillar, uvular, pharyngeal	155	71	84	54%
Tonsillar, pharyngeal, nasal	255	76	179	70%
Tonsillar, pharyngeal, tracheobronchial	24	0	24	100%

In Table III the location of the diphtheria membrane among 472 of the myocarditis patients is set forth together with the results of treatment. The tonsillar cases in which the absorption of toxin from the site of the membrane is least rapid show the lowest death rate, whereas those with nasal involvement have the greatest number of fatal terminations if the tracheobronchial cases, in which the unfavorable outcome is primarily due to asphyxia, are excluded.

In Chart 1 is shown the distribution of 303 of 308 fatal cases according to the number of days from onset on which death ensued. Here it

may be seen that 79 per cent of the myocarditis deaths occurred within the first two weeks of the illness while but 21 per cent occurred later. As a matter of fact the period during which the development of myocarditis in the average case of diphtheria is to be most feared is from the tenth day to the fourteen day of the disease. It is at this very time often that the patient appears to be entering the stage of convalescence and recovery seems assured. Notwithstanding this assertion it may be seen in the chart pertaining to deaths in our series that the greatest number of deaths occurred on the sixth day of disease.

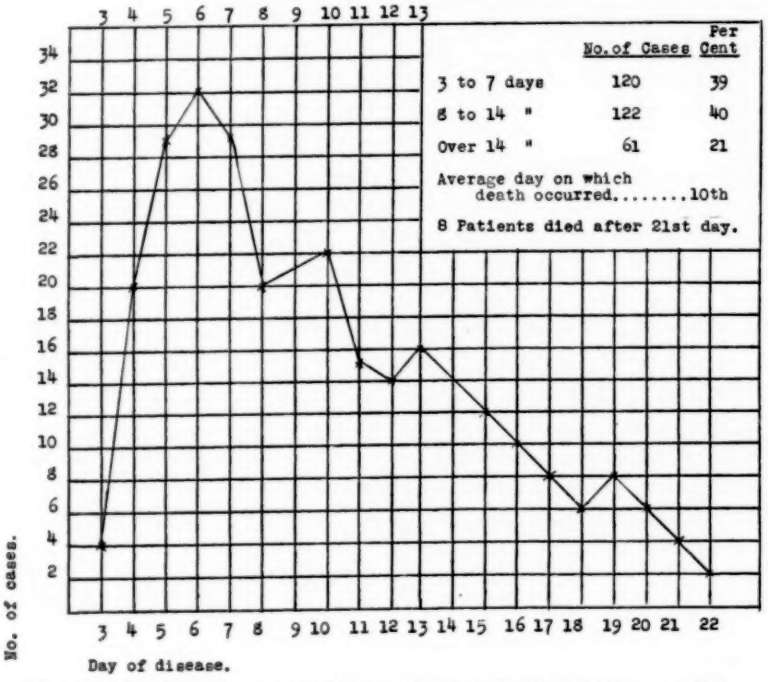
No. of cases.
Day of disease.
No. of Cases
Per Cent
3 to 7 days 120 39
8 to 14 " 122 40
Over 14 " 61 21
Average day on which death occurred.....10th
8 Patients died after 21st day.

Chart 1.—Day of disease on which death occurred from diphtheritic myocarditis.

This apparent contradiction is explained in the first place by the unreliability of the history as it concerned the date of onset. Frequently a diphtheria patient was suffering from the disease for several days before the illness was recognized. Secondly, in the malignant type of diphtheria, myocarditis sometimes manifested itself very early.

Abdominal pain is often the first signal to cause alarm to the clinician experienced in the care of diphtheria. If abdominal pain is accompanied by vomiting, it usually means that death is stalking the patient and the end is not far away even though the general appearance of the patient may be good. Restlessness is another bad omen. In most

instances bradycardia is pronounced with the onset of myocarditis although sometimes the pulse may continue to be very rapid and weak throughout the course of the disease. In ninety-one instances in which vomiting was recorded, seventy-six of the patients died and fifteen recovered. Albuminuria and an enlarged and tender liver were also signs of grave prognostic importance, as well as pronounced cervical adenitis.

Jordan[3] has called attention to the marked increase in diphtheria morbidity during 1926-1927 which took place in widely separated localities. Germany, Italy, France and Spain experienced a sharp rise in both morbidity and mortality from this disease. In England also the greater incidence was apparent, as for example in Leeds, where the case fatality rate rose from 3.3 per cent in 1928 to 9.2 per cent in 1931. In this country the experience of Detroit and Chicago was somewhat similar as observed in the contagious disease hospitals.

At a time when the general conclusion was being reached that diphtheria was soon to be permanently subdued by means of active immunization, this perplexing increase in prevalence and virulency developed. In many instances criticism was directed toward the antitoxin used for treatment because of its apparent failure to save lives. As a partial explanation for some of these circumstances, Anderson, Happold, McLeod and Thomson[4] endeavored to show that diphtheria may be due to one of two different types of organism. *Bacillus diphtheria gravis* was presumed to be the causative factor in malignant diphtheria while *bacillus diphtheria mitis* was responsible for the milder infections. It was only in the latter cases that marked response to diphtheria antitoxin was notable.

CLINICAL FINDINGS

The primary clinical abnormality used to establish a diagnosis of myocardial damage was a change in the character of the heart tones, especially a softening of the first heart sound in the mitral area. The persistence of tachycardia or bradycardia was an almost constant finding. Bradycardia was always a grave prognostic sign. Of seventy-six patients having a pulse rate below 66, thirty-nine recovered and thirty-seven died. There were nine cases with a rate below 50, only one of which recovered.

Alterations in the heart rhythm to a gallop type frequently developed during the first three days. Extrasystoles were so common as to be the rule. Enlargement of the liver occurred in practically every case to a greater or less degree. A systolic murmur was noted in 118 cases or approximately 25 per cent. Enlargement of the heart as evidenced by a migration of the apex beat and the left heart border to the left of the midclavicular line was found in an equal number of cases.

One of the most distressing features was the mental anguish of these patients. They were comfortable in no position for more than a few minutes at a time and continually shifted themselves in bed. They were often tortured by thirst, fluids given by mouth being constantly returned.

Blood pressure readings below the normal limits were obtained in all severe cases and were usually unchanged in the milder types. The lowest systolic blood pressure in a case recovering from myocarditis was 44. A diastolic blood pressure reading as low as 0 was not infrequent. The average blood pressure readings are shown in Chart 2.

ALBUMINURIA

Albuminuria was a frequent finding in cases of diphtheritic myocarditis. In 392 cases in which the urine was examined 262 or 66 per

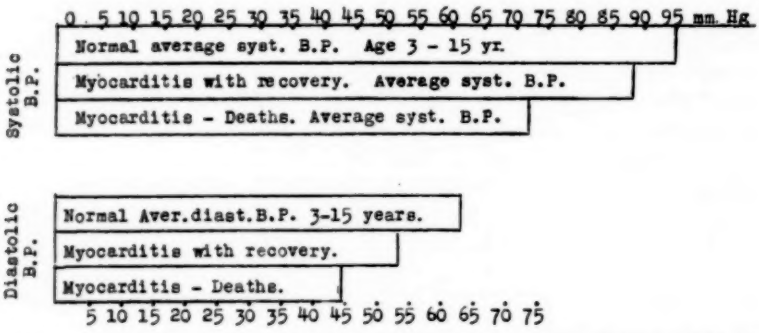
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 mm. Hg.
Systolic B.P.
Normal average syst. B.P. Age 3 - 15 yr.
Myocarditis with recovery. Average syst. B.P.
Myocarditis - Deaths. Average syst. B.P.
Diastolic B.P.
Normal Aver.diast.B.P. 3-15 years.
Myocarditis with recovery.
Myocarditis - Deaths.
5 10 15 20 25 30 35 40 45 50 55 60 65 70 75

Chart 2.—Blood pressure in diphtheritic myocarditis as compared with normal blood pressure.

cent, showed albuminuria. Albuminuria was present in 84 per cent of the patients who died. Of those that recovered 52 per cent had albuminuria as shown in Table IV.

TABLE IV

ALBUMINURIA IN DIPHTHERITIC MYOCARDITIS

	POSITIVE ALBUMIN	NEGATIVE ALBUMIN	PERCENTAGE POSITIVE ALBUMIN
Recoveries	93	85	52
Deaths	169	32	84

The frequency with which albuminuria occurred in these cases was somewhat significant from a diagnostic and prognostic standpoint. That is, albuminuria so frequently preceded the onset of symptoms referable to myocarditis that when a patient showed an albuminuria for the first time, we could predict with reasonable certainty that that

case would later develop signs of myocardial weakness. Furthermore, when a patient who was progressing favorably developed albuminuria the prognosis immediately became grave. Albumin when present in the urine usually occurred in large amounts. Three- or four-plus albuminuria was more frequent than one- or two-plus. Blood and casts occurred in the urine only occasionally.

PATHOLOGY

Autopsies were performed on 126, or approximately one-half of the patients dying of circulatory failure. The pathologic changes were extensive and profound. The heart in each case was a pale greyish color, having the appearance of boiled meat. The heart muscle was soft, dilated, flabby, translucent, tearing easily. There were hemorrhagic areas varying in size from a pinpoint to a pinhead scattered throughout the myocardium and pericardium. The lungs and liver showed marked passive congestion. A diphtheritic membrane lined the tracheobronchial tree in twenty-four cases which one of us has previously reported in detail.[5] The liver was frequently enlarged to the level of the umbilicus and showed marked evidence of toxic changes. The pancreas revealed intense congestion with many petechial hemorrhages scattered through the gland. The kidneys showed extensive cloudy swelling. In the suprarenal glands, hemorrhages were found in more than one-half of the cases, the hemorrhages frequently spreading to involve the perisuprarenal tissue. The left suprarenal was found to be hemorrhagic in a much larger number of cases than the right gland. As pointed out by Edmunds and Johnston,[6] this severe injury to the suprarenals producing a decrease in output of epinephrine may be a contributory factor in circulatory failure in diphtheria. The essential pathology, however, classically described by Warthin,[7] and which we believe was the true cause of death in each of our cases, was the marked myocardial change in the form of a toxic parenchymatous degeneration. We wish to emphasize that in each case which came to autopsy the cause of death was accounted for on the basis of a severe myocarditis.

DRUG AND SERUM THERAPY

For many decades epinephrine and caffeine have been the drugs most commonly used as circulatory stimulants in the treatment of diphtheritic myocarditis. Possibly due to tradition or maybe for want of some better form of treatment, these drugs were used in 239 patients or approximately one-half of our cases of myocarditis. Epinephrine, although it frequently raised the blood pressure and often strengthened the pulse, was so transitory in its action that a permanent beneficial effect was found wanting. Since epinephrine and caffeine sodium benzoate both act by whipping up the heart, we

question if their use may not be contraindicated in a heart condition in which rest should play such an important rôle. It may be significant in this connection that the largest number of recoveries, taking all types of the disease into consideration, occurred among the group that were treated only with absolute rest in bed, with good food and good nursing care.

Much has been written regarding the dosage of antitoxin in grave cases of diphtheria. Some authorities have advocated as much as 200,000 and 300,000 units of antitoxin in severe cases. Reliable statistics, however, have shown the mortality rate has not been decreased by such huge doses of antitoxin. Others have advised combining diphtheria antitoxin with antistreptococcic serum on the grounds that malignant diphtheria is caused by a combined diphtheria and streptococcus infection. This combined serum treatment, too, failed to give convincing results.

In this series of cases, the amount of antitoxin administered varied according to the location and extent of the membranous lesions. As a rule, 50,000 units was the maximum dose used. This amount was reserved for cases with extensive membrane covering the tonsils, uvula, pharynx, and nasal mucosa. Simple tonsillar diphtheria received from 10,000 to 20,000 units. Cases with nasal involvement never received less than 20,000 units and frequently 40,000 units were administered. The results obtained from these moderate dosages seemed in every way equally as satisfactory as the very large doses. In severely toxic cases, antitoxin in the amount of 10,000 units was administered intravenously while the remainder was given intramuscularly.

GLUCOSE THERAPY

Edmunds and Cooper[8] in 1925 reported the favorable results obtained when glucose was injected intravenously into dogs in which a severe diphtheritic myocarditis had been produced. They found that if they could get glucose solution into the circulation before the heart stopped, no matter how critical the condition of the dog at the time, "the animal would be revived and serve for the investigation of the effects of various drugs used in similar conditions." Following the injection of glucose, they reported a marked increase in the strength of the heart. The pulse became stronger and stronger until it compared favorably with that produced by the normal heart. In many cases the authors state, "the glucose was life-saving." The results were much superior to those obtained from the use of epinephrine, digitalis, and the pituitary preparations. They ascribed the beneficial results from the use of glucose as "probably due to the nutritive value on the heart muscle, the glucose acting as a source of energy." Furthermore, Lereboullet[9] and others have shown that in a considerable

number of severe cases of diphtheritic myocarditis a definite hypoglycemia was present.

In view of these observations, we thought it might be of value to determine clinically the effects of intravenously injected glucose on the most severe cases of myocarditis, especially since the cardiac stimulants most commonly used seemed in our experience to be definitely contraindicated.

One hundred and twelve patients presenting grave symptoms of diphtheritic myocarditis were given repeated intravenous or intramuscular injections of a 10 per cent glucose solution. In children under five years of age the intramuscular route was substituted for the intravenous route. The amount of each injection varied from 100 to 200 c.c. Each patient received from two to nine injections. The treatment was not used in any mild or moderately severe cases. The patients in which glucose was administered were all critically ill, and in some instances almost moribund.

It is difficult to describe completely all the essential points by which one determines the condition of a patient suffering from diphtheritic myocarditis. In an analysis such as this, it becomes necessary to resort chiefly to a description of the most important clinical findings and compare them with those found after treatment with glucose.

Almost immediately following the administration of glucose, there was noted an increased strength in the heart tones. A thready pulse became markedly stronger. In many cases an increase in the systolic blood pressure of from 5 to 10 mm. of mercury was noted. Relief from discomfort and distress was frequently observed, and patients would volunteer the information that they felt much better after receiving glucose. Many of these patients were in a condition of impending death. There was a waxy pallor to the skin. They were almost pulseless, unable to speak. They were in a condition of severe circulatory collapse. Following the glucose injection, they would open their eyes, their color would improve, and they would return to consciousness. They would even attempt to raise themselves up to the sitting position. As Woodcock[13] has aptly described the condition, "They appear to be recovering while at the same time they are really dying." This improvement following glucose therapy was not always permanent; the patients, after a few hours, had a relapse to their former condition of collapse, and the heart beats gradually became imperceptible. Not infrequently, however, they could be restimulated by repeated injections of glucose.

In some patients there was a spectacular recovery apparently attributable to glucose therapy, as the following case report will illustrate:

A three-year-old boy was admitted to the hospital on the seventh day of diphtheria. A necrotic membrane covered the tonsils, the uvula, the pharynx, and

the nasal mucous membrane. There was constant bleeding from the nose and mouth, with petechial hemorrhages into the skin. He had a "bull-necked" type of cervical adenitis. The temperature was 101° F., and the pulse was 130 but of fair quality. The first heart tones were good. The systolic blood pressure was 60 and diastolic 0. He was extremely toxic and in a critical condition. He was given 50,000 units of antitoxin immediately on admission to the hospital. On the following day the heart tones were very distant and weak. The pulse was of poor quality. He was in a semicomatose condition due to profound toxemia. There was enlargement of the liver two fingers below the costal margin. Because of his desperate condition and rapidly failing heart, he was given 6 minims of adrenalin every four hours with no apparent improvement. Glucose therapy was then instituted by giving 100 c.c. of a 10 per cent glucose solution intramuscularly as well as liberal amounts of glucose by mouth and per rectum. On the following day the blood pressure was 60/50. The first heart tones were scarcely audible. There was marked irregularity with frequent premature beats and pulse rate of 168. He was waxy and comatose. The intramuscular injection of 100 c.c. of 10 per cent glucose was repeated following which the patient opened his eyes, smiled, and answered questions intelligently for the first time since admission to the hospital. The blood pressure rose to 70/50. Following further glucose therapy the heart condition showed a slow but definite improvement as evidenced by a stronger pulse, fewer premature beats, and a return of pinkness to his cheeks.

On the fourteenth day after his admission, or the twenty-first day of the disease, he developed paralysis of the soft palate and muscles of deglutition so that all foods had to be fed by gavage. Two days later he developed paralysis of neck and back muscles. Despite these new complications, his heart condition continued to improve gradually so that we were able to discontinue glucose therapy on the seventh day after admission. He was discharged after fifty-two days in the hospital as entirely recovered with the exception of occasional extrasystoles.

Of the 112 cases of severe myocarditis treated with glucose, there were ten recoveries. One might question the efficacy of any form of treatment in which there was a recovery rate of only 9 per cent of the treated cases. However, when one takes into consideration that we were dealing with a group of cases that already had been referred to as malignant diphtheria, we felt that glucose therapy was not entirely in vain. Due to the severity of these cases, death would probably have supervened in practically every instance had not glucose been administered.

BLOOD SUGAR ESTIMATIONS

Lereboullet, Marie, and Leprat[9] showed that in a considerable proportion of cases of grave diphtheria, definite hypoglycemia was present, while in the mild and moderate cases the blood sugar content was unaltered. Schwentker and Noel[10] recently reported that severe cases showed hyperglycemia in the early stage with a hypoglycemia developing in the later stages. On the basis of this altered carbohydrate metabolism, these workers have attempted to explain the cause of circulatory failure in diphtheria.

Coincident with our study of glucose therapy, blood sugar determinations were made in twenty-nine cases of severe diphtheritic myocarditis. Fifty-five blood sugar estimations were made in all. The first blood sugar determination on each patient was made during the fasting period and the second at varying intervals after the intravenous or intramuscular injection of glucose. Eleven cases showed a fasting blood sugar above 120 mg. The balance, or eighteen cases, showed a blood sugar within normal limits. Fasting blood sugar values ranged from 80 mg. to 152 mg. per 100 c.c., the average being 110 mg. Following the intravenous or intramuscular injection of glucose, there was a definite and sharp rise in the blood sugar as shown in Table V.

TABLE V

BLOOD SUGAR ESTIMATIONS IN DIPHTHERITIC MYOCARDITIS BEFORE AND AFTER GLUCOSE ADMINISTRATION

PATIENT	AGE	FASTING BLOOD SUGAR MG. PER 100 C.C.	INTERVAL BETWEEN GLUCOSE ADMINISTRATION AND 2ND BLOOD SUGAR ESTIMATION	BLOOD SUGAR AFTER GLUCOSE INJECTION MG. PER 100 C.C.
L. B.	5	111	2 hr.	133
F. J.	11	112	3 hr.	181
F. B.	13	142	----	----
J. B.	4	86	2 hr.	76
J. D.	5	108	20 min.	138
L. L.	8	200	2 hr.	85
C. J.	8	85	24 hr.	141
L. N.	8	130	3 hr.	173
R. W.	5	137	15 min.	230
M. N.	10	87	1 hr.	100
H. J.	11	141	2 hr.	144
F. O.	6	114	3 hr.	123
A. B.	5	151	3 hr.	242
G. W.	2	106	5 hr.	243
L. C.	2	86	½ hr.	107
F. K.	3	137	1 hr.	182
C. W.	34	152	30 min.	178
I. P.	5	111	3 hr.	123
E. C.	5	105	45 min.	156
G. M.	12	111	2 hr.	128
M. B.	12	100	30 min.	128
J. D.	7	101	15 min.	120
C. H.	2	80	15 min.	228
C. N.	12	114	2 hr.	157
F. R.	10	99	1 hr.	102

The average increase in blood sugar was 40 mg. per 100 c.c. These findings are in accord with those of Rosenthal[11] who found that following the ingestion by diphtheritic rabbits of 20 gm. of glucose, the blood sugar rose to a definite hyperglycemia and returned to normal only after many hours. Hector[12] showed similar results in clinical cases of severe diphtheria.

This marked hyperglycemia persisting as it did for many hours after glucose injections may indicate that there was a marked decrease in the capacity of patients with toxic diphtheria to assimilate dextrose from the blood stream. This was probably due to the suppression of the production of insulin caused by the toxic effect of diphtheria on the pancreas. Pathologic findings, which have previously been referred to, showed that the pancreas was severely damaged.

If there was a decreased insulin output in these cases, the use of glucose with insulin in the treatment would suggest itself. Favorable results from the use of glucose-insulin therapy have been reported by several investigators, within the last two or three years. Woodcock[13] claimed improvement in the patients' conditions with relief from discomfort and distress. Schwentker and Noel[10] treated fourteen cases with glucose and insulin and had thirteen recoveries. Toomey[14] found the use of dextrose decreased the incidence of heart-block and acute dilation in diphtheritic myocarditis, but, although in the presence of heart-block life was prolonged, none of his patients with heart-block treated with dextrose recovered.

So far the number of cases treated with glucose or with glucose and insulin has been too small to permit any fully developed conclusion regarding the value of such therapy in severe diphtheritic myocarditis. Nevertheless, the results seem sufficiently favorable to justify these procedures.

SUMMARY

1. In 496 cases of myocarditis which developed in 4,671 diphtheria patients, there was a fatality rate of 62 per cent.

2. The fatality rate was 75 per cent during the age period from one to five years; 54 per cent, from six to ten years; 50 per cent, from eleven to fifteen years; and 43 per cent, over fifteen years of age.

3. The mortality was highest (70 per cent) in cases in which there was nasal involvement and lowest (11 per cent) in simple tonsillar diphtheria.

4. Seventy-nine per cent of all deaths from diphtheritic myocarditis occurred during the first fourteen days of the disease, the average day on which death occurred being the tenth.

5. Abdominal pain and vomiting with falling pulse rate and blood pressure were signs of grave prognostic importance.

6. "Malignant diphtheria" was an important factor in accounting for the high mortality rate.

7. The most important pathologic findings in 126 autopsies was extensive toxic myocardial degeneration.

8. Epinephrine and caffeine were of no value as permanent circulatory stimulants.

9. Parenterally injected glucose solution seemed to be a life-saving measure in some cases of severe diphtheritic myocarditis.

10. A series of blood sugar determinations before and at varying intervals after glucose administration are presented.

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RHEUMATIC ENCEPHALITIS (CHOREA INSANIENS)

A Case Report With the Use of Avertin Therapy

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ENCEPHALITIS in relation to acute infectious diseases is now a well-established fact, and such terms as "postvaccinial encephalitis" or "measles encephalitis" have become increasingly familiar to physicians within the past few years. However, the term "rheumatic encephalitis" has not yet been commonly used. Nevertheless, the case to be presented can best be classified under such a nomenclature; for here the relationship of the rheumatic virus to the cerebral involvement is certainly an exceedingly close one. The protean clinical symptoms in Sydenham chorea indicate a widespread involvement of the central nervous system, and pathologic studies by various authors tend to point toward a definite inflammatory process within the brain. We say tend advisedly, because the pathology of acute chorea is complex and still somewhat uncertain. One of the reasons for this lies in the scarcity of autopsy material, inasmuch as death due to acute chorea alone is rare. Until Marie and Tretiakoff[1] in 1920 reported their complete findings in a case of Sydenham chorea, there was but very little known pathology of this condition in so far as the central nervous system was concerned. These authors described findings in their case identical with those seen in patients who had died of epidemic encephalitis. In fact, Wilson and Winkelman[2] in their report on the pathology of acute Sydenham chorea are inclined to wonder whether Marie's case should not have been classified as one of the choreiform type of epidemic encephalitis. These latter authors describe a case of acute chorea in a girl, twelve years old, who had an indefinite short clinical history with physical findings typical of rheumatic chorea and an associated endocarditis. Autopsy showed vegetations on the auricular side of the mitral leaflets, but a thorough and systematic examination of the brain with modern staining methods and with special reference to the basal ganglia failed to reveal any specific lesions. It was true that the vessels of the brain were all markedly congested, but not more than is usually found in a patient dying of an infectious disease; no thrombotic vessels were found nor were any alterations noted in the subthalamic or cortical regions. On the other hand, Lhermitte and Pagniez[3, 4] in an extensive review of the literature show a definite but variable pathologic basis for chorea. They present a detailed study of

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a young woman, aged nineteen years, whose illness commenced in early November and progressed as a typical chorea to death in December. Grossly there was evident congestion of the meninges. A summarization of their very detailed microscopic examination is as follows: Vasodilatation, vascular rupture and capillary hemorrhage, distention of the adventitial sheaths by an albuminous exudation and cellular changes—tigrolysis and karyolysis, with the gradual reduction of the cytoplasm and the final destruction of the cell. As to typography, the lesions were predominant in the dentate nucleus, putamen-caudate segment of the striate body, and the Perkinje cells of the cerebellar cortex.

On the basis of their studies, they believe that acute chorea can be divided into two groups: one characterized by more or less diffuse inflammatory lesions and the other, in which degenerative processes predominate. A later study by van Gehuchten[5] agrees with this conception of Lhermitte but states that the diversity of opinion among other workers in this field depends principally on the duration of the process in the particular case studied. When a disease has lasted only a few days, inflammatory lesions are found; and when it has lasted from one to two months, degenerative lesions are seen. He reports a study in a boy, aged fifteen years, in whom chorea was present for fifteen days before death. The histology of the brain showed a transition between inflammation and degeneration. Fresh inflammatory regions were found in the corpora quadrigemina and red nucleus; beginning degenerative lesions were noted in the dentate nucleus and Perkinje cells of the cerebellum where the inflammatory processes were already subsiding; while definite degenerative areas were found in the thalamus, caudet nucleus, putamen, and certain parts of the cerebral cortex. It would thus seem that the primary and essential lesions in chorea are in the basal ganglia, from where the toxic processes spread caudad.

The case to be presented shows the clinical features of a widespread severe involvement of the central nervous system occurring simultaneously with rheumatic cardiac involvement. It is also of interest because of the type of therapy instituted, the employment of a nonvolatile anesthetic to control the wild motor activity.

REPORT OF CASE

History.—S. J., eleven and one-half-year-old female, was admitted to the Children's Service of the Beth Israel Hospital, March, 1933, with the story that nine days prior to admission she had an upper respiratory infection, i.e., coryza and mild cough, associated with a temperature of 103° F. for two days. This was followed on the fourth day with painful swellings of the right and left wrists and left ankle joint. These pains and swellings persisted, in a gradual milder degree, up to the time of admission to the hospital.

Her past history had two significant factors: following an attack of measles four years before, she had a mild attack of polyarthritis, which cleared up after a short period in bed; then, one year before the present admission she had a mild attack

of scarlet fever during the first week of which there also occurred pain and slight swelling in the joints. In between these two attacks she had always felt perfectly well and was a happy, active normal child.

Examination.—The admission physical examination revealed a well-nourished child, seemingly not very ill, with moderate tenderness and some limitation of motion of the knees, left ankle, both wrists, and small joints of the hand. The throat was congested and granular; the tonsils had been removed. The heart was regular, moderately rapid, and there was a soft systolic murmur at the apex, not transmitted to the left; the second pulmonic sound was somewhat accentuated. A teleroentgenogram showed no cardiac enlargement. However, an electrocardiogram revealed an inverted T-wave in Leads I and II, changes which were interpreted as being due to myocardial involvement, no digitalis medication having been given. The blood count showed moderate anemia (hemoglobin, 63 units Sahli; R.B.C., 3,450,000); and leucocytosis of 15,300 cells, with 81 per cent polymorphonuclear cells. The sedimentation rate upon admission was 90 mm. in forty-five minutes, using a Weiss tube in which the upper limit of normal is 12 mm. in forty-five minutes. Her temperature upon admission was 104° F. The case was considered to be one of rheumatic fever of the polyarthritic type, and, because of the joint pains, sodium salicylate was administered, the dosage being 20 grains every four hours. The initial course was one of rapid improvement; the temperature dropped to normal within six days; the joints rapidly cleared up so that all medication was stopped on the eighth day, and the child was apparently in good condition with normal temperature and a slow regular heart, at the apex of which there was heard a soft systolic blow.

The child continued to do well until the twelfth day after admission, when the temperature rose to 100° F. The heart became more rapid, and slight choreiform movements were noted. Sedimentation rate at this time had dropped to 25 mm. Simultaneous with the onset of chorea there appeared a scarlatiniform rash, which within twenty-four hours had involved the entire body, and which persisted for six days with gradually decreasing intensity. Some petechial spots were observed over the abdomen and lower extremities on the third day after the appearance of the rash. Because of the previous history of scarlet fever, the pale throat at this time, and the negative Schultz-Charlton blanching test, the rash was diagnosed as being a toxic erythema. The blood culture taken the first day after its appearance was reported as sterile.

During all of this first week of chorea the temperature was gradually rising, so that by the end of that period it ranged between 103° F. and 105° F. daily. At the same time, the choreiform movements became rapidly more and more violent, which together with severe emotional outbursts gave the terrible picture of raving mania. The ordinary sedatives (barbital group) and morphine in moderate sized doses were of no value in controlling this condition. Ulcerations of the buttocks and about the heels and ankles developed because of the violence of the movements, and the child's condition was rapidly growing worse from this combination of marked muscular activity associated with high temperature and lack of food and fluids. The skin was dry, the heart was rapid with sounds of poor quality, and there was marked cyanosis. On the fifth day of her chorea it was decided to use the nonvolatile anesthetic avertin to produce rest and sleep. This was administered per rectum in a dosage of 80 mg. per kilogram of body weight. Within fifteen minutes there was a remarkable change; all the choreiform movements had ceased and the child was in a quiet sleep which lasted about eight hours. During this period she received subcutaneous injections of glucose and saline and was also able to take some fluid by mouth during the latter part of this narcosis. As the avertin was

wearing off, the sedative effect was continued by means of paraldehyde (5 c.c.) also given rectally. As a succeeding dose of paraldehyde became less effective and the maniacal chorea again became manifest, the avertin therapy was again instituted. This mixture of avertin and paraldehyde succeeded in keeping the child in a relatively semistuporous condition during the second week. During this period her temperature continued to mount, and ranged between 103° F. and 106° F. daily. The condition of her heart was interesting; whereas previously there was heard only a soft systolic blow at the apex, there began to be noted a definite pericardial friction rub. An electrocardiogram also showed a beginning heart-block, the P-R interval being 0.28 second. Her skin condition previously noted had cleared up by the end of this week, but there was observed a red, hot, tender area over the outer part of the right foot. A second blood culture was also reported as sterile. Because of the hyperpyrexia and the evident rheumatic condition, salicylate therapy was again begun. On one day she was given 80 grains of sodium salicylate without any effect, and on the next day this was followed by twenty grains every two hours for six doses, with no appreciable change. In fact, just following the cessation of this therapy, her temperature rose to 108.4° F., and the child was comatose and markedly cyanotic. A spinal tap showed fluid under slightly increased pressure with a one-plus globulin, normal sugar, and 70 cells per cubic millimeter, 80 per cent of which were lymphocytes. Blood analysis showed a moderate nitrogen retention (NPN 46 mg. per 100 c.c.), normal glucose; and a spectroscopic examination for methemoglobin was negative. An x-ray picture of the chest showed a beginning pericardial effusion; the lungs were clear. This extreme hyperpyrexia seemed to mark the turning point of the disease, for during the third week the choreiform movements became slightly less marked and the temperature assumed a lower level, ranging between 101° and 104° F. daily. The child was semiconscious during the greater part of this period, and blood transfusions and hypodermoclysis helped to maintain her nutrition. The pericarditis increased, so that at the beginning of the fourth week of her illness there was an effusion which by x-ray examination showed the left cardiac border to be in the posterior axillary line. There was, however, no real circulatory embarrassment. A pericardial tap to determine the character of the fluid was unfortunately contaminated, the fluid being mixed with traumatic blood. As the fourth week of her illness drew to a close, there was a definite improvement; the chorea was less marked, and the child began to show some slight response to command. There was noted at this time a right facial paralysis, and a peculiar facial grimace was associated with any attempt to follow a command.

By the middle of the fifth week practically all choreiform movements had ceased, but the child was left with a rigid facial expression, especially the eyes, which were held in a fixed downward stare. A neurologic note by Dr. E. D. Friedman very aptly describes the condition. He stated, "The eyes are held in a fixed downward gaze with inability for ocular motor activity in any direction. There is definite facial asymmetry, especially right-sided weakness. The deep reflexes are hyperactive, and there is a bilateral Babinski present. The motor weakness is diffuse in character, probably due to both nervous fatigue and central nervous system involvement. There is definite evidence of emotional instability. The impression is one of a widespread encephalitis which has most markedly involved the basal ganglia. The eye condition is remarkable in that it is further evidence of basal ganglion disease affecting oculomotor control."

The further course was one of slow but gradual improvement, both so far as the pericarditis and nervous system involvement were concerned. The fixed expression of the face disappeared during the seventh week, and the ocular motor movements returned to normal within ten days thereafter. The child sat up in bed at the end

of the eighth week and was discharged from the hospital three and one-half months after admission, with nothing to show for her severe illness except a slight systolic murmur at the apex.

SUMMARY

This case presents the picture of a most severe type of chorea, so-called chorea insaniens, occurring very shortly after the course of a rather mild acute rheumatic fever. The involvement of the central nervous system was widespread and severe, as evidenced by the most marked motor activity and severe emotional disturbance, as well as the hyperpyrexia and cyanosis, which were also probably of cerebral origin. During the course of this severe nervous disturbance, there was progressive cardiac involvement, indicated first by an incomplete heart-block, followed by a definite pericarditis with effusion. Most interesting were the residual nervous phenomena after the acute central nervous system involvement had subsided; these phenomena consisted of a fixation of the eyeballs in a downward gaze, with inability for ocular motor activity in any direction—an evidence of basal ganglion disease affecting ocular motor control. Because of our newer knowledge of the pathology of chorea, the clinical features of this case, and its close relationship to the rheumatic virus, the designation of this condition as rheumatic encephalitis seems justified.

Cases which have been designated as chorea insaniens have an exceedingly high mortality. Death, if not due to toxemia, is usually caused by marked exhaustion, the result of the wild motor activity and lack of nourishment. In this case, after other sedatives had failed to produce any result, rest and relaxation were brought about through the use of avertin, a nonvolatile anesthetic. It was during such quiet periods that nourishment and other therapeutic aids could be administered. This procedure certainly seemed life-saving during the critical period of this case, and it is urged that it be tried in similar situations.

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ENDOCRINE STUDIES IN INFANTS AND CHILDREN

I. Methods of Procedure and Diagnostic Criteria

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THE advances in the knowledge and scope of endocrinology in the past decade have been so extensive as to permit the paraphrasing of the old medical adage, "Know syphilis and you know medicine," into "Know endocrinology and you know medicine."

The time has arrived when endocrinology must take its place as a recognized integral phase of medicine and be subject to study and evaluation by the same rigid criteria as any other field. This necessarily includes standardization of diagnostic procedures. The methods advanced by Rowe in the chemical and laboratory approach and by Engelbach in clinical procedure have done much to crystallize the situation, but they are both too exhaustive and too expensive for practical application by the general practitioner in the diagnosis of endocrine conditions in infants and children.

A plan of diagnostic approach is offered in the latter age group which has been utilized by the writer and his associates in whole or in part in the study of over 1,000 children in the Endocrine Clinics of the Long Island College Hospital and the Israel Zion Hospital. It can be carried out in any office or clinic if properly equipped for this type of investigation. We acknowledge our indebtedness to Rowe and Engelbach.

The present communication consists of three parts: (1) methods of endocrine survey, (2) diagnostic criteria of endocrine conditions in infants and children, and (3) case reports illustrating the diagnostic procedure and interpretation.

Part I

METHODS OF ENDOCRINE SURVEY

CASE NO.: LONG ISLAND COLLEGE HOSPITAL

FINAL DIAGNOSIS: ENDOCRINE CLINIC

HISTORY

Name: *Date:* *Sex:*

Address: *Referred by:* *Color:*

Age: *History Supplied by:*

Chief Complaints: Time of inception, duration, progress.

From the Department of Pediatrics, Long Island College of Medicine and the Endocrine Clinics of the Long Island College Hospital and the Israel Zion Hospital.
Read before the Buffalo Academy of Medicine, November 22, 1933.

Family History:

1. Familial incidence of endocrine and nonendocrine disorders (goiter, diabetes), stature, obesity, malformations, mental retardation, psychoses, etc.
2. Mother's history with special reference to condition preceding, during and following birth of patient
3. Other children: number, state of health, development, etc.

Personal History:

1. Birth:
   a. Numerical position in family
   b. Age of parents at time of birth of patient
   c. Duration and type of pregnancy and labor
   d. Condition and weight at birth
2. Developmental:
   a. Physical: Time of holding head erect, sitting unaided, crawling, teething, walking, talking (words and sentences)
   b. Mental: Normal, precocious, or retarded. If mentally retarded, the time when first noted and relationship to illness
   c. Genital and Sexual: Normal, precocious, or retarded; abnormalities; secondary sex characteristics (genitals, hair, voice, body) (If menstruation has begun, give full details)
3. Feeding and Previous State of Nutrition: Length of time of breast feeding, type of feeding, present diet; weight and height curves
4. Illnesses: Contagious diseases, continued fevers, trauma, operations, etc., with dates and details as to outstanding sequelae
5. Special Symptoms: Increase or decrease in weight, cessation of growth, sudden increase in rate of growth, change in body contour, increase in size of neck, appearance of hair in abnormal locations or in abnormal amount, obesity, drowsiness, etc. Age at which first noted and relation to any infection, trauma, or operation
6. Neurologic: Paralyses, gait, convulsions, tremors, myopathies, etc.
7. Habit Formation: Eating, drinking (amount of fluid intake during day), sleep, bowels, urination [polyuria, enuresis (diurnal, nocturnal)], speech (vocalization, comprehension), masturbation, and sex curiosity
8. Social Behavior: Social attitude in general (leader, mixer, bully, asocial), temper, tantrums, obedience, adaptability, lying, stealing, obstinacy, cruelty to children and animals
9. Personality Reaction: Seclusiveness, timidity, sensitiveness, fearfulness, cowardice, imagination, daydreaming, selfishness
10. Schooling: Age at entrance, present grade, progress, impression of teachers, effort, concentration, muscular coordination, manual work, poor subjects, special interests, social adjustments
11. Social Conditions at Home: Type of home, social scale, relationship to parents and other children

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PHYSICAL EXAMINATION

NAME: CASE NO.:

DATE:

A. *General Appearance:*

1. Type
2. Nutrition
3. Muscular tone and development

4. Posture and gait
5. Distribution of fat
6. Mentality

B. *Skin:*

1. Texture
2. Color
3. Eruptions and pigmentations
4. Hair—distribution and amount in detail

C. *Head and Face:*

1. Contour
2. Fontanel
3. Symmetry
4. Size
5. Appearance

D. *Nose:*

E. *Ears:*

F. *Eyes:*

1. Pupils
2. Vision
3. Ptosis
4. Nystagmus
5. Appearance (equidistant, Mongolian, etc.)
6. Strabismus
7. Exophthalmos
8. Fundus and fields if necessary

G. *Mouth:*

1. Lips
2. Palate
3. Teeth (number, consistency, arrangement, size, caries, etc.)
4. Malformations

H. *Neck:*

1. Type of neck (long, short, etc.)
2. Thyroid
3. Supraclavicular fat pads

I. *Thorax:*

1. Formation
2. Localized adiposity
3. Breasts
4. Lungs
5. Heart

Pulse: Blood Pressure: Before exercise
After exercise

6. Thymus
7. Hair (axilla, chest)

J. *Abdomen:*

1. Contour
2. Fat distribution
3. Masses
4. Points of tenderness
5. Liver, spleen, and other viscera

K. *Genitals:*
1. Conformation
2. Size (phallus, testes, scrotum, clitoris, labia)
3. Abnormalities (cryptorchidism, pseudohermaphroditism, etc.)
4. Pubic hair (type of escutcheon, distribution, and amount)
5. Pubic fat

L. *Lymphatic System:*

M. *Extremities:*
1. General conformation
2. Hands
3. Feet
4. Fingers
5. Tremors

N. *Measurements:* Weight Height
1. Circumference of head (above eyebrows)
2. Circumference of chest (at nipple line)
3. Circumference of abdomen (at navel line)
4. Upper longitudinal measurement (vertex of head to top of pubes)
5. Lower longitudinal measurement (top of pubes to sole of heel)
6. Span

O. *Neurologic:*

P. *Mental:*
1. Psychometric and achievement tests as indicated (special forms)

Q. *Special:*
1. Reactions (adrenalin, pituitrin, pilocarpine, etc.)
2. Electrocardiograms
3. Capillaroscopy
4. Shadowgram
5. Photograph
6. Other examinations

INSTRUCTIONS FOR PATIENTS FOR THE ENDOCRINE WORK-UP

1. *For the Basal Metabolism Test:*
Have an early supper the night before the test without any kind of meat, fish or cheese.
Go to bed at least by 10 o'clock the night before the test.
Have at least ten hours of sleep.
Ride to the hospital. *Do not walk.*
Come to the hospital without any breakfast.

2. *For the Specific Dynamic Action Test:*
Do the same as for the above test except for the following breakfast: The whites of three hard boiled eggs, one thin slice of toast without any butter, and a cup of weak tea without any sugar, cream, or milk.

3. *For the Blood Chemistry and Blood Count:*
Come to the hospital without any breakfast.

4. *For the Salt Retention Test:*
a. Collect all the urine passed in the twenty-four hours in the following way:
(1) On getting up in the morning empty the bladder and discard the urine passed.
(2) Eat your usual breakfast.

(3) Urine is collected from then on including the first urine passed the next morning before breakfast.

(4) Bring *all* the urine collected to the laboratory with a list of foods eaten that day. Label "Bottle 1."

b. On the following day repeat the same diet of the previous day.

(1) After finishing breakfast, take the 10 grams of salt which are prepared in capsules.

(2) Collect all the urine for the entire day also including the first specimen of the next morning.

(3) Bring *all* the urine to the laboratory. Label "Bottle 2."

5. *For the Sugar Tolerance Test:*

Come to the hospital without any breakfast.

LABORATORY REPORT

NAME: CASE NO.:

DATE:

Urine:

Amount	Specific Gravity	Sugar
Before NaCl	Before NaCl	Urea N
After NaCl	After NaCl	Urobilinogen
Total Nitrogen	NaCl	Acetone
Albumin	Before	
Microscopic	After	

Blood Count:

Red Blood Cells	Hemoglobin (per cent)	Immature (per cent)
White Blood Cells	Polymorphonuclears (per cent)	Eosinophiles (per cent)
Lymphocytes (per cent)	Monocytes (per cent)	Sedimentation
Abnormal Cells		

Blood Chemistry: (Mg. per 100 c.c. of blood)

Urea N	Creatinine	Uric Acid
Sugar	Cholesterol	Chlorides
Calcium	Phosphorus	

Serology:

Wassermann

Sugar Tolerance:

Amount given:

Blood Sugar:	Fasting	½ hr.	1 hr.	2 hr.	3 hr.
Urine:	Fasting	½ hr.	1 hr.	2 hr.	3 hr.

X-ray Findings:

Thymus	Carpal and epiphyseal development
Sella	Osseous System

Metabolism:

B.M.R.	M.R. After protein meal	Specific dynamic action

SUMMARY SHEET

NAME: CASE NO.:

DATE:

History:

Examination:
1. Physical
2. Mental

X-ray Findings:

Laboratory Findings:
1. Metabolism
2. Chemistry
3. Blood count

Glands Involved: (Designate functional activity by plus or minus signs)

A. Pituitary:
1. Anterior lobe
   a. Sex hormone
   b. Growth hormone
   c. Thyrotropic hormone (specific dynamic action of proteins)
   d. Miscellaneous functions: uric acid, lymphocytes, etc.
2. Posterior lobe
   a. Carbohydrate metabolism
   b. Fat metabolism (considered by Evans, Anselmino, and Hoffmann et alia to be the function of the anterior lobe)
   c. Salt metabolism (blood and urine)
   d. Water metabolism

B. Thyroid:
1. Development: Physical Mental Bone
2. Basal metabolism

C. Gonads:
a. Primary or secondary involvement
b. Primary sex organs

D. Other Glands:

NAME: CASE NO.:

DATE:

FINAL DIAGNOSIS:

RECOMMENDATIONS:

A. *Therapy:*

B. *Diet:*

C. *General Instructions:*

PROGRESS NOTES

NAME: CASE NO.:

DATE:

Chief Complaints:

Developmental:

A. Physical: Teething, walking, talking

B. Mental: Obtained from mother and school authorities
Achievement and intelligence tests
Behavior

C. Osseous: Carpal and epiphyseal growth

General: Appearance
Weight
Height Other measurements

Local:	Fat distribution
	Hair distribution
	Secondary sex changes
Laboratory:	Chemistry studies
	Basal metabolism and specific dynamic action of proteins
	Blood pressure and pulse
Photograph:	(Every six months)
Therapy:	

Part II

DIAGNOSTIC CRITERIA

Chief Complaints.—A study of our case records show the following to be the chief complaints and the reasons for referring a child to an endocrine clinic:

1. Retarded physical development manifested by late teething, sitting, walking, or talking.
2. Retarded mental development ranging from dullness in school to definite idiocy.
3. Growth disturbances, generally short stature. Accelerated growth is very rarely the cause for referring a child unless accompanied by other disturbances, such as mental retardation, obesity, or hypogonadism.
4. Sex disturbances manifested by hypoplasia of the external genitals or cryptorchidism in boys or delayed puberty in girls. The reverse conditions of precocious puberty are not as frequent.
5. Excessive obesity in both sexes with or without genital hypoplasia.
6. Behavior disorders, psychoses, and neuroses.
7. Goiter.
8. Slimness.

History.—The history of endocrinopathies in parents has been placed by some authorities as high as 20 per cent, but it is much below this in our series of 600 children with various endocrine disorders. Tuberculosis, syphilis, alcoholism, consanguinity, and neuropathy are not of great etiologic importance. The past history of the mother is especially important. Four periods of her life should be investigated for possible relationship to infantile hypothyroidism: (1) the physical development in the first year of life, (2) mental and physical progress during the infantile and juvenile periods, (3) the presence of a colloid goiter during adolescence, menstrual irregularities, fatigability, and chlorosis, (4) thyroid response during previous pregnancies shown by thyroid enlargement, pallor, nausea, and vomiting. The basal metabolic rate should be taken in every suspicious case and an absence of 15 per cent increase after the third month of gestation should lead to an investigation of thyroid function. Women who have experienced a hypothyroid state should be warned against a possible recurrence

in future pregnancies. Women may give birth to a normal child, develop a goiter or myxedema, and then give birth to a hypothyroid child subsequently.

The incidence of multiple cases of any particular endocrine disorder seems to be greatest in adiposogenital dystrophy, pituitary-thyroid obesity in girls, childhood myxedema, hypothyroidism, and anterior pituitary deficiency in the order named. There is no predilection for any numerical sequence in the family of endocrine disturbance. The age of the parents and the type and duration of pregnancy and labor are not of any etiologic importance.

The rate of physical and mental development serves as one of the most important criteria in the diagnosis. Normal eruption of teeth, walking, sitting, holding the head erect, and talking is found in adiposogenital dystrophy, thyropituitary obesity, goiter, anterior pituitary deficiency, hypogonadism, and giantism but is markedly delayed in childhood myxedema, hypothyroidism, and mongolian imbecility. Mental retardation occurring in the first year of life in both the endocrine and nonendocrine groups (including mongolian imbecility) delays the subsequent rate of both physical and mental development.

All deviations from the normal mental progress should be investigated with special reference to the chronologic relationship of the mental retardation to physical development, illness, trauma, operation, and the clinical endocrine picture. A knowledge of the progress at school, the social attitude of the child, and the results of previous organotherapy on mental retardation and behavior is essential.

Mental retardation may be noted at birth (as in childhood myxedema and mongolism), after an illness, operation, or trauma, or appear insidiously during childhood. In our series, hypothyroidism and mental retardation appeared in higher than normal frequency after scarlet fever, measles, pneumonia, whooping cough, diphtheria, "fever," and acute thyroiditis. Pituitary disturbance and mental defects followed whooping cough, encephalitis, epileptic seizures, and falls.

The history should include detailed description of all special symptoms which may be of endocrine import such as increase or decrease in weight, obesity, slimness, cessation of growth, sudden increase in rate of growth, change in body contour, increase in size of neck, appearance of exophthalmos, appearance of hair in abnormal amounts or localities, sudden increase in appetite, etc. A knowledge of all fevers, illnesses, operations, and trauma is essential in reference to the time of occurrence of endocrine symptoms.

Adiposity and increase in weight may appear at birth, following an acute illness, trauma or operation, or at puberty.

An infant who weighs more than eight pounds at birth may be the subject of either hypothyroidism or hypopituitarism. In the former

there is subsequent delay in physical and / or mental development while in the latter it is normal. Both types continue to be obese, but the thyroid child shows a greater tendency to lose weight after the first few years.

There is a definite relationship between pituitary obesity and illness, trauma, and operations in our series, the endocrine condition occurring with the greatest frequency in the following sequence: after tonsillectomy, encephalitis, whooping cough, epileptic seizures, fall, measles, and operations other than tonsillectomy.

Neurologic symptoms such as paralyses, gait, and convulsions are not of endocrine origin but may be associated with nonendocrine mental retardation. Tremors are found with hyperactivity of the thyroid.

Excessive eating and drinking may be exogenous in nature but are often manifestations of hypopituitarism and adiposogenital dystrophy. Polyuria and polydipsia are characteristic of the same conditions and may be due to an actual diabetes insipidus or a disturbed water metabolism. Eneuresis may be the result of a neurosis, habit formation, local irritation, or hypoactivity of the thyroid or pituitary glands.

Constipation and sluggish bowels are present in hypothyroidism and hypopituitarism while a tendency to loose movements may be produced by the reverse glandular activities.

Physical Examination.—The severity of the clinical manifestations of any endocrine condition depends primarily upon the degree of glandular activity and secondarily upon the age at which the deficiency appeared.

There is a disturbance of growth in childhood myxedema, hypothyroidism, anterior pituitary deficiency, adiposogenital dystrophy, and endocrine infantilism. An increased height is found in eunuchoidism, giantism, and preadolescent acromegaly. Acromegaly is very rare in this age period. The stature depends upon the functional activity of the growth hormone of the anterior lobe. Deficiency in the growth hormone is much more frequent than an increased activity.

Extreme slimness is found in eunuchoidism, hypogonadism, status thymolymphaticus, marked hyperthyroidism, thin type of hypothyroidism, pituitary cachexia (Simmond's disease) and anterior pituitary deficiency. Obesity may be due to exogenous causes like overfeeding, or to hypothyroidism, hypopituitary deficiency, pituitary-thyroid dysfunction, hyperpituitarism as a result of basophilic adenoma, hyperplasia or neoplasm of the adrenal cortex, and hypogonadism.

Thyrogenous obesity is of universal distribution with a tendency toward localization in the supraclavicular region. This is associated with other signs and symptoms of hypothyroidism, such as delayed development, retarded ossification, dry skin, etc.

The hypopituitary type is characterized by adiposity with a predilection for the breasts, abdomen, buttocks, subscapular, and suprapubic regions. The extremities are usually free from superfluous fat in contrast to the thyrogenous type, but at times there may be a pronounced general obesity as well. The accumulation of fat varies, but even in the absence of actual adiposity the distribution is found in the characteristic regions. There is a history of normal physical and mental development.

Pituitary-thyroid obesity is usually found in female children and is manifested by a normal developmental history, fat distribution of the hypopituitary type, chemical changes characteristic of pituitary deficiency, and a lowered basal metabolic rate. The latter is due to a secondary hypothyroidism or to a deficiency of the thyrotropic hormone of the anterior pituitary lobe. In male children there is a tendency to a female contour and a high waistline; the genitals may be normal or hypoplastic.

The hyperpituitary type has been recently described by Cushing as being due to basophilic adenoma of the anterior pituitary lobe and is confined to the face, neck and trunk; the extremities are spared. There is also sexual dystrophy and hirsutism on the face and trunk in both sexes.

The adrenal type of obesity is due to hyperplasia or neoplasm of the adrenal cortex and occurs in two forms—the obese in female children and the Herculean in male. Marked hirsutism and signs of premature puberty are present in older children but generally not in female infants.

Obesity due to primary hypogonadism is never observed at birth, and seldom in childhood prior to puberty. In young eunuchoids, the general appearance is that of tall, graceful girls but there may be localized fat distribution on the outer thighs, hips, breasts, and hypogastric regions. The obesity in secondary hypogonadism is probably of pituitary origin.

Cutaneous changes have been found in various endocrine conditions. The dry skin of hypothyroidism and the brownish discoloration of Addison's disease are familiar to all, but in addition eczema, ichthyosis, and scleroderma may be of thyrogenic origin; vitiligo may be due to pituitary deficiency and psoriasis may be a manifestation of thymic inactivity. Recklinghausen's neurofibromatosis with cutaneous pigmentation has been found to be associated with childhood myxedema, hypothyroidism, and pituitary and adrenal dysfunction.

Disturbance in hair growth and distribution are observed in thyroid, pituitary, gonadal, and adrenal diseases and may be local or general. In hypogonadism, eunuchoidism, and status thymolymphaticus there is deficiency in growth of hair on the body, face, and extremities, but

that on the scalp is usually long and sparse. These disturbances do not appear in children until puberty. Alopecia may be due either to thyroid or pituitary deficiency.

The scalp hair in childhood myxedema and hypothyroidism is dry, coarse and sparse, or thin and scanty. The thinning of the outer-third of the eyebrows is not always present nor does its occurrence necessarily indicate hypothyroidism. In adiposogenital dystrophy the scalp hair is generally soft in texture, oily, and abundant; the eyebrows are shaggy.

Generalized hypertrichosis affecting the face and body is found in hyperadrenalism, hypergonadism, and hyperpituitarism as a result of either hyperplasia or neoplasm of these organs. In the gonadal and adrenal types, which occur more frequently in the female, there is a pronounced growth of both lanugo-like and permanent hair on the chin and face margin with at times a heavy mustache and beard. The chest shows hair between the breasts and nipples in the female; the abdominal and pubic hair is heavy and in the female assumes a masculine escutcheon; the pudendal and perineal regions are covered with thick, long hair. The extremities are covered with a thick, coarse type of hair which at times is as long as that found in the axilla or over the mons. In hyperpituitarism, the distribution of generalized hypertrichosis remains true to the sex type of the individual. There may be alopecia of the vertex of the head.

Disturbances of the hair may be indigenous to the race and family of the patient and are not always necessarily endocrine in origin.

Some of the eye disturbances in endocrine conditions are exophthalmos in hyperthyroidism, retinitis pigmentosa with polydactylism and developmental anomalies in adiposogenital dystrophy, cataract in mongolism, and visual field changes in pituitary neoplasm.

Examination of the teeth must take into consideration the time of eruption, number, placement, consistency, size, and tendency to decay. In thyroid deficiency there is retardation in the laying down of the embryonic tooth buds and their eruption. The teeth are small, thin, brittle, transparent and are short-lived because of a tendency to decay. The second set are crowded and malocclueded. There seems to be a relationship between the size of the teeth and the general body growth. Both the deciduous and permanent teeth are small and slender in infantilism, anterior pituitary deficiency, and hypogonadism. In hypogonadism the lateral upper incisors are smaller than the rest, or they may be congenitally absent. In pituitary types the teeth in general are firmer in consistency and longer lived than in the thyroid type. There are two types seen in adiposogenital dystrophy: in the short Frölich form the teeth are short, firm, and well formed with large upper central incisors; in the tall Cushing-Neurath type they are large,

well formed, firm in consistency, densely calcified, and separated. The upper central incisors are large and the lateral incisors are small.

In the examination of the neck the presence or absence of a goiter is to be noted. Goiter in children may be congenital, juvenile, or adolescent according to the age at which it appears and may be colloid, adenomatous, or exophthalmic depending upon the pathology present. The gland is generally hypoactive and nontoxic in the congenital type, hypoactive or normal in the colloid, juvenile, and adolescent types and hyperactive in the adenomatous and exophthalmic forms.

Hyperthyroidism is manifested by emotional instability, general nervous irritability, mental overactivity, fine tremor of the fingers, excessive sweating, tachycardia, extreme hunger, slimness or loss of weight, and occasional diarrhea. The gland may or may not be perceptibly enlarged. Substernal thyroid enlargement is rare in children.

Simple acute thyroiditis may occur during the course of an acute infection or menstrual period but the gland subsequently returns to normal size and function. Recurrences may result in a permanent hyperplasia.

The condition of the primary sex organs and secondary characteristics are to be noted. Pseudohermaphroditism is considered to be due to fetal hyperplasia of the suprarenal cortex. The internal sex organs designate the true sex of the individual, and the external genitals are usually of the opposite sex.

Pubertas praecox may be due to hyperplasia or neoplasm of the adrenal cortex and of the pineal and gonads during infancy or childhood. There is also an unclassified group of an unknown etiology.

Primary hypogonadism (eunuchoidism) is rare in the preadolescent age. Secondary hypogonadism occurs with adiposogenital dystrophy, infantilism of both the pituitary and thyroid glands, childhood myxedema, hypothyroidism, and status thymolymphaticus. Cryptorchidism may be due to deficiency of the thyroid or pituitary glands.

The extremities are long in primary hypogonadism and short in hypothyroidism and hypopituitarism. The spade hand is found in acromegaly; the long hand in giantism, and the small petite hand in infantilism and anterior pituitary deficiency. The short pudgy hand is found in hypothyroidism. The fingers tend to taper in adiposogenital dystrophy, but we have all noted this tendency in normal infants and children. The incurving of the little finger is very frequently noted in mongolian imbecility, but it is not limited to this disease. The prehensile toe occurs in mongolian imbeciles and other nonendocrine types of mental retardation, but it is not pathognomonic of any one condition.

Engelbach and coworkers have stressed the importance of anthropometric measurements in endocrine conditions. They have formulated standards for the various age periods which may be utilized independently or in conjunction with those of Baldwin and Wood, Woodbury, Pirquet, Lucas, and others. Special attention is paid to the height, weight, span, upper and lower longitudinal measurements, and circumference of the head, chest, and abdomen.

Mentality.—Every child with mental retardation, neurosis, psychosis, and behavior disorder should be subjected to an endocrine survey. The incidence of endocrine disease in these conditions is placed in the literature between 10 and 15 per cent, but this is not conclusive as it includes cases "due to" and "associated with" endocrine dyscrasia.

In a study of the mentality of about 1,000 children in the Endocrine Clinics, we found that mental retardation occurs with greater frequency in association with nonendocrine conditions than with endocrine. Only 25 per cent of the total number of mentally retarded children manifest some signs of endocrine disturbance. The degree of mental retardation is more marked in the nonendocrine group as shown by the occurrence of 50 per cent of this type in the lower zones of mentality with an I.Q. of 50 or less as compared with 10 per cent in the endocrine group.

In analyzing the degree of mentality present in the 529 children in the endocrine group, we found that 50 per cent have a normal mentality; 20 per cent are dull or backward in school, and 30 per cent have an I.Q. of 75 or below.

The incidence of the various endocrine conditions in mentally retarded children is in the following sequence: childhood myxedema, hypothyroidism, adiposogenital dystrophy, thyropituitary obesity, and hypogonadism. Behavior disorders occur more frequently with pituitary disease than with any other endocrine condition.

Further analysis will endeavor to divide the endocrine group into two subdivisions: those cases in which the mental retardation is due to the endocrine condition and those associated with it.

Roentgenology.—Investigation of bone development should be carried out in every suspected endocrinopathic patient under eight years of age and in every case of juvenile mental retardation.

Retarded ossification is found in childhood myxedema, endemic cretinism, and hypothyroidism and may be noted as early as birth by the absence of centers of the knee and ankle. There is delay in epiphyseal closure in infantilism and eunuchoidism, but the carpal centers are normal. Premature ossification is noted in hyperactivity of the adrenal, gonad, pineal, and pituitary glands. Normal bone development occurs in hypopituitary disorders and goiter.

There is no accord as to what constitutes the normal size or weight of the thymus. These differ materially with the age and general body conditions to such an extent that standards have not as yet been adopted. A child presenting a clinical picture of the so-called thymic asthma in association with a large thymic shadow should be given the benefit of thymic radiation.

The sella turcica may be round, oval, or flat in shape. There are no variations in the shape or size of the sella turcica in mongolian imbecility or in any endocrine disease which are characteristic for that disease. It may be eroded by tumors of the pituitary region.

In every osteopathy localized in one bone, a thorough x-ray study and clinical examination of the rest of the skeleton should be made for signs of hyperparathyroidism (rarefaction and depletion of calcium of bone and occurrence of multiple cystic tumors).

Metabolism.—The five standards of basal metabolism: total calories referred to height, sitting height, to weight, to surface area, and to age seem to bear a fairly constant relationship to the total metabolism of normal children, but the findings are subject to certain limitations.

The detailed discussion of these limitations cannot be entered into at this time, but suffice it to say that the same significance and reliability cannot be placed upon the rates in this age group as in adults. Additional factors are the inability to keep the child in a true basal state because of fear, excitability, and lack of cooperation, especially in those under seven years of age and in the mentally retarded.

The casual, solitary test is not of very great value. An increased rate cannot be interpreted as being due to hyperthyroidism unless the above mentioned factors have been eliminated. A low basal rate does not always signify a hypothyroid state as it has been reported in asthma, epilepsy, malnutrition, starvation, and following infections. It may also be due to deficiency of the thyrotropic hormone of the anterior pituitary lobe.

The basal metabolic rate is not always an indicator of the degree of thyroid activity or of the severity of the symptoms. It is of great assistance in controlling treatment as improvement is generally indicated by a rise in the rate of the normal. At times, however, symptoms of overdosage due to hyperthyroidism may develop before the rate reaches the normal.

We have found the Aub-DuBois and the Benedict-Talbot standards to be most satisfactory for children.

The determination of the specific dynamic action of protein is of value in the diagnosis of pituitary disease. The method modified by Goldzieher and Gordon is as follows: The basal metabolism is established by the usual technic. On the following morning or on the same day, a test meal is given consisting of the whites of three hard boiled

eggs, a slice of toast without any butter and a cup of tea without sugar, cream, or milk. The metabolism is again determined after two hours of rest and the difference between the preprandial and postprandial readings is considered as the rate of specific dynamic action of proteins. In normal individuals this is from 10 to 35 per cent above the initial B.M.R. It is markedly diminished or absent in deficiency of the metabolic hormone of the anterior pituitary lobe and increased in hyperactivity of this lobe in tumors.

Blood.—Lymphocytosis occurs normally during childhood but in the pubescent and adolescent periods may signify an endocrine imbalance especially a deficiency of the adrenal and pituitary glands. Anemia is found in myxedema, hypothyroidism, and hypoadrenalism. Eosinophilia is present in pituitary hypofunction but also in allergic conditions and with intestinal parasites in normal children.

The relationship between sedimentation time and endocrine conditions especially with reference to the basal metabolic rate has not been definitely established. An increased sedimentation rate has been reported in hyperthyroidism and a decreased rate in hypothyroidism.

The Wassermann test should be made in all children with endocrine conditions as a routine measure. There is a difference of opinion as to its incidence and etiologic significance, but our personal observations tend to minimize the importance of congenital syphilis as a factor in the production of any endocrine condition.

The chemical changes in the various endocrine disorders are as follows: Only one type of disturbed function of each gland is mentioned for the sake of brevity. The findings are reversed in the opposite conditions.

In hypothyroidism we find a tendency to a fasting hypoglycemia, increased sugar tolerance, and a high blood cholesterol. In hypopituitarism, anterior lobe deficiency, we find a high uric acid content of above 3.5 mg. per 100 c.c. of blood, which is unaccompanied by renal or hepatic disorders. The chemical changes due to the posterior lobe deficiency of the pituitary gland are (a) high blood chlorides (above 500 mg. per 100 c.c. of blood), (b) salt retention (determined by the difference in the amount of NaCl present in the urine before and after the ingestion of 10 gm. of salt). In normal individuals all the salt should be eliminated in the 24 hours. The normal NaCl content in the urine of children in our series is 7.1 gm., (c) water retention as shown by the failure to excrete an increased volume of urine following the ingestion of 10 gm. of salt, (d) tendency to a fasting hypoglycemia, and (e) an increased sugar tolerance. The chemical changes which are found in hyperparathyroidism are as follows: hypercalcemia (from 12 to 19 mg. per 100 c.c. of blood serum), hypophosphatemia, increased urinary phosphorus and calcium output, and

disturbance of calcium balance. (Under normal conditions, from 70 to 90 per cent of calcium is excreted in the feces and from 10 to 30 per cent in the urine, but in hyperparathyroidism these conditions are reversed; from 70 to 90 per cent is excreted in the urine and from 10 to 30 per cent in the feces. Patients with hyperparathyroidism cannot maintain a calcium equilibrium on a normal calcium intake which is 0.45 grams of calcium daily.) In hypoadrenalism the following are the changes: tendency to a fasting hypoglycemia, increased sugar tolerance, and an increase in the blood nitrogen metabolites (uric acid, urea, and creatinine).

Special Examinations.—Electrocardiogram: Small or absent P and T waves have been described in myxedema while normal electrocardiographic curves have been found in infantilism, hypogonadism, and mongolism.

Numerous investigators have reported the following as characteristic signs in patients with low basal metabolic rates: Low P wave in Lead II, low R in all leads, low T in Lead II, inverted T in one or more leads, delayed auriculoventricular conduction, and spread and notched QRS waves.

The electrocardiogram curve is considered in conjunction with the so-called "myxedema heart" described by Zondek, Fahr, and others which is manifested by an enlargement and symptoms of cardiac decompensation which do not respond to therapy by rest and digitalis but are cured by thyroid extract.

Capillaroscopy: Abnormal capillary loops have been reported in hypothyroidism, myxedema, mongolian imbecility, and mental retardation.

Abderhalden reaction: The ferment reaction of Abderhalden and the estimation of the exchange of gases are utilized by European investigators but not by many in this country to determine the function of the various endocrine glands both quantitatively and qualitatively. The two modifications of the Abderhalden reaction in use are the refractometer of Pregl and the interferometer of Hirsch.

Female Sex Hormone: The female sex hormone and the anterior pituitary hormone are found in the umbilical cord blood, urine, and blood of the newborn. They are also present in the blood during childhood and prepubescent period but in too small amounts to be of any clinical significance.

Androtin: The male sex hormone (androtin) is absent in the urine of boys under ten years of age but is present in that of adolescent boys and mature men. It is, of course, absent in hypogonadism in the latter two age groups.

As pointed out by Rowe, laboratory findings serve only as confirmatory evidence and should never take precedence over clinical observations. No single test can be regarded as significant unless it be checked

and controlled by a number of other independent observations. It should not be used to support a diagnosis until all other possible non-endocrine causes have been eliminated.

Part III

ILLUSTRATIVE CASE OF CHILDHOOD MYXEDEMA

Chief Complaint.—Failure to grow physically and mentally.

History.—J. R., four years old, was the last of thirteen children. There was no history of goiter in the mother, but a sister, aged eighteen months, was also suffering from childhood myxedema. Both of these children were born after the mother was forty years old and in spite of abortifacts employed during both pregnancies. The mother attributes their condition to the use of these drugs. All of the other children are of normal intelligence except for a sister, twelve years old, who is mentally retarded with an I.Q. of 75 but with no signs of hypothyroidism.

The mother states that only three of her babies weighed less than 9 pounds; two weighed 14 and 15 pounds. The patient weighed 10 pounds and was delivered normally at full term, nursed for fourteen months, held his head erect at six months, began teething at fourteen months, walking at two and one-half years, and talking at four years. He had not progressed beyond a few unintelligent words at the time of the first visit. The mother sensed he was not developing normally after he had passed his second birthday.

The child had always been sickly, suffering from whooping cough at two months, active rickets during his first two years, frequent attacks of upper respiratory infection at three and one-half years. He was operated upon for tonsillectomy and adenectomy at three years. Constipation has been marked since birth.

Physical Examination.—He was brought to the clinic with his sister on May 29, 1931. The child was of short stature with a marked general, structural, and muscular underdevelopment. The arms were relatively long and the legs short and bowed. The skin was rough and dry with a pale, waxy, myxedematous color but without eruptions or pigmentation.

The head showed a tendency toward macrocephaly with a flattening of the vertex. The forehead was low and presented pronounced frontal bossae. The eyes were normal except for narrow palpebral fissures. The fontanels were closed; the hair was thin, dry, and scant on the head. The face was rounded and dull looking; the nose was saddle shaped; the lips were thick and everted; the tongue was enlarged and protruding from a gaping mouth. The teeth were small, thin, irregular, and separated. The throat was negative.

The neck was short and rested upon a fairly well-developed chest, with flaring and beading of the ribs. There was a slight increase in supraclavicular fat padding. The thyroid was not palpable. The lungs and heart did not present any abnormalities.

There was a definite "pot belly" with an umbilical hernia and exaggeration of the posterior lumbar curve. The abdomen did not reveal any further abnormal findings except for bilateral inguinal hernias. The external genitals were commensurate with the age of the child in size and appearance. The extremities were cold to the touch.

Mental examination by a psychologist revealed a mental retardation with an intelligence quotient of 50.

	MEASUREMENTS	NORMAL ACCORDING TO ENGELBACH
Weight	28 lb.	31.8 – 39.2 lb.
Height	32.5 in.	38.8 – 41.6 in.
Span	35.4 in.	37.3 – 40.3 in.
Upper measurements	18.2 in.	21.6 – 23.2 in.
Lower measurements	14.2 in.	16.8 – 18.4 in.
Circumference of head	21.7 in.	21.1 in. (Optimal)
Circumference of chest	21.7 in.	21.4 in. (Optimal)
Circumference of abdomen	20.2 in.	20.0 in. (Optimal)

X-ray Findings.—Examination of the long bones. Elbows—there were no epiphyses present; wrist—no epiphyses or carpal centers present. Normally there should be two carpal bones and the ossification center in the lower end of the radius at about six months. Knees—there was a small center in the epiphysis of the upper end of the femora. These measured about 1.5 cm. in the longest diameter. These two epiphyseal centers are present two days after birth usually but should be larger than those described at six months. Ankle—apparently only three tarsal centers present, and there was a smaller center in the epiphysis in the lower end of the tibiae. These are normally present at about five months of age. Hip joints—no epiphyseal centers present. There should be a moderate-sized center of ossification present in the epiphysis for the head of the femur at eleven months. Skull is normally outlined. There is no evidence of increased intracranial pressure. Sella turcica is small, round, and shows no evidence of erosion. Examination of the thymus does not reveal any enlargement. There is a slight broadening of the epiphyseal line in the lower end of the tibia with suggestion of saucerization.

Laboratory Data.—

A. Urine: Reaction, acid; color, amber; specific gravity, 1,015; sugar, albumin, and acetone, negative; indican, a trace; bile pigment, hemoglobin, negative; microscopic, a few epithelial cells and calcium phospate crystals.

B. Blood Count: Hemoglobin, 85 per cent; leucocytes, 7,000; erythrocytes, 4,840,000; polymorphonuclear leucocytes, 27 per cent; lymphocytes, 67 per cent; monocytes, 3 per cent; eosinophils, 1 per cent; basophils, 2 per cent.

C. Blood Chemistry: N.P.N. 31.6 mg.; Urea N, 11.2 mg.; uric acid, 2.3 mg.; sugar, 93.3 mg.; protein, 8.7 mg.; cholesterol, 307 mg.; chlorides, 598 mg.; calcium, 10.4; phosphorus, 4.3 mg.

D. Wassermann test was negative.

Summary

History: One sister with childhood myxedema and an older sister with mental retardation. History of retardation in both physical and mental fields.

Examination: Typical picture of childhood myxedema with mental retardation.

X-ray: Pronounced retardation of osseous development. Bone developmental age was estimated at less than six months. Rickets was present.

Laboratory: High blood cholesterol and high blood chlorides.

Glands Involved.—Thyroid: Hypofunction expressed by:

1. Delay in physical, mental, and osseous development
2. Typical appearance
3. High blood cholesterol.

Pituitary: Anterior pituitary lobe may be secondarily involved and its deficiency expressed by:

1. Delay in body growth
2. High blood chlorides.

Final Diagnosis.—Childhood myxedema; rickets.

Recommendations.—1. Thyroid therapy beginning with gr. $\frac{1}{10}$ and increasing to gr. i t.i.d.

2. Anterior pituitary extract beginning with gr. ii and increasing to gr. v t.i.d.

3. Antuitrin 1 c.c. twice a week

4. Cod liver oil, viosterol, and appropriate diet.

ILLUSTRATIVE CASE OF ADIPOSOGENITAL DYSTROPHY WITH HYPOTHYROIDISM

Chief Complaint.—Infantile genitals with obesity.

History.—A full-term normal delivery child with a birth weight of 5 pounds and 14 ounces; breast fed for fourteen months. Previous illnesses included mumps, German measles, slight colds, and pyelitis. Patient began to teeth at the age of fifteen months, walk at fifteen months, talk at ten months, and sit at nine months. He began to gain weight rapidly at the age of five years. Habits were normal with the exception of polydipsia. Behavior was normal. Retardation in school with very poor concentration.

Physical Examination.—Overdeveloped with a general distribution of fat especially about the mammae, abdomen, subscapular, and trochanteric regions. Posture was good; muscular tone was good; patient appeared mentally normal. The skin was moist; hair, moist with a slight hypertrichosis. No eruptions or pigmentations on the skin. Eyebrows were well developed. Mouth showed a high arched palate; teeth small, firm in consistency, and separated on the lower jaw. Tonsils were slightly hypertrophied. Neck was short. Thyroid was palpable; lungs, negative. Systolic murmur which is not transmitted was heard. Breasts were overdeveloped. The abdomen was of the "Michelin" type. Genitals were infantile; testicles, undescended. Extremities revealed long hands which tended to taper. The patient was seven years old.

	MEASUREMENTS
Weight	79¾ pounds
Height	49 in.
Circumference of chest	29 in.
Circumference of abdomen	30 in.
Upper measurements	25 in.
Lower measurements	24⅜ in.
Span	49 in.

X-ray Findings.—Wrist: Five small carpals and small epiphyses of the ulna, first metacarpal, and radius; bone texture, normal; sella turcica, normal in size and oval in shape.

Laboratory Data.—A. Basal Metabolism: B.M.R. before protein meal, –25 per cent; M.R. after protein meal, –25 per cent; specific dynamic action, 0.

Blood Chemistry: Urea N, 14.6 mg.; glucose, 78 mg.; cholesterol, 218 mg.; uric acid, 4.6 mg.; chlorides, 560 mg. per 100 c.c. of blood.

Blood Count: Erythrocytes, 4,000,000; leucocytes, 6,100; hemoglobin, 79 per cent; polymorphonuclears, 45 per cent; lymphocytes, 48 per cent; monocytes, 4 per cent; eosinophils, 2 per cent.

Sugar Tolerance: One hundred grams of dextrose given. Fasting specimen, 80 mg.; ½ hour, 144 mg.; 1 hour, 140 mg.; 2 hours, 115 mg.; 3 hours, 75 mg. Urine was negative for the four hours.

Salt Retention Test: Amount for twenty-four hours, 380 c.c.; amount for twenty-four hours after the ingestion of 10 gm. of salt, 480 c.c.; specific gravity, 1.030 and

1.022, respectively; NaCl output for twenty-four hours, 2.9 gm.; NaCl output for twenty-four hours after the ingestion of 10 gm. of salt, 4.2 gm. Urine examination negative for albumin, glucose, and acetone.

Summary

History: Late development in teething and walking.

Examination: Typical appearance of adiposogenital dystrophy with increased growth. Mentality, normal.

X-ray Findings: Slight retardation in bone development. Sella turcica is normal.

Laboratory Findings: Low basal metabolic rate and a specific dynamic action of zero. Chemistry shows high blood chlorides, high uric acid, high blood cholesterol, low blood sugar, normal sugar tolerance, salt retention, and water retention. Blood count is within normal limits.

Glands Involved.—Pituitary Gland:

A. Anterior lobe:
   1. Sex hormone—deficiency with secondary hypogonadism
   2. Growth hormone—increased activity
   3. Specific dynamic action—decreased function
   4. High blood uric acid content—expression of deficiency of lobe.

B. Posterior lobe:
   1. Carbohydrate metabolism—disturbed function expressed by low blood content
   2. Salt metabolism—deficiency of functional activity expressed by high blood chlorides and urinary salt retention
   3. Fat metabolism—deposit of fat throughout body may be due to posterior lobe deficiency or anterior lobe deficiency with salt and water retention
   4. Water metabolism disturbance expressed by polyuria, polydipsia, and water retention.

Thyroid Gland: Deficiency expressed by:
   1. Delayed physical development
   2. Slight delay in osseous development
   3. Low basal metabolic rate

Final Diagnosis.—1. Adiposogenital dystrophy due to bilobar pituitary deficiency.
2. Hypothyroidism.

Recommendations.—1. Therapy by mouth t.i.d. for three weeks and discontinue for one week of each month.

	1st Month	2nd Month	3rd Month	4th Month
Anterior Pituitary Extract	gr. ii	gr. iii	gr. v	gr. v
Thyroid Extract	gr. ⅛	gr. ¼	gr. ½	gr. i

2. Intramuscular injections antuitrin, 1 c.c. twice a week.
3. Diet: high protein, low carbohydrate, low fat, salt free, and restriction of water intake.

SUMMARY

Every case of suspected endocrinopathy should be given a complete survey from the following viewpoints: Family and past personal history, physical examination, x-ray study, and laboratory findings, the latter to include the morphology and chemistry of blood and urine and metabolic rates. The latest advances in this field have been made with

the aid of the laboratory, but these serve only as confirmatory evidence and should never take precedence over clinical observations.

The paper presents forms of methods of procedure in the diagnosis of endocrine conditions in children, a discussion on diagnostic criteria and two illustrative cases in which these methods are employed.

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Critical Review

TUBERCULOSIS IN CHILDREN

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IN THE two previous reviews attention has been directed chiefly to setting forth the newer concepts of tuberculosis in children with particular reference to the primary or first infection type in comparison to the adult or reinfection type. That the fundamental facts distinguishing these two disease processes have been quite generally accepted is well attested to by the numerous articles[1-15] which have appeared in the literature in the past year. To review each of these seems unnecessary, although many of them are excellent and frequently give personal experiences of the author in tuberculin testing or interpretation of roentgenograms, which are distinct contributions to our knowledge.

Myers[16] states that the first infection and reinfection types of tuberculosis are as different as though caused by two distinct microorganisms. It seems essential to the success of the battle being waged against the tuberculosis foe that the great mass of practicing physicians of the country clearly appreciate these differences and fully comprehend the significance of related factors. In this regard Hawes[17] says, "We will never do more than scratch the surface in case finding until we sell the idea to the general practitioner that it is his duty to test by tuberculin and to x-ray every member of the family, but especially the children, where he finds a case of pulmonary tuberculosis." Whenever the physician secures a history of contact with a human case of tuberculosis, he should assume the child has been infected until he has proved the contrary by repeated tuberculin tests applied over several months of time after contact has been broken. Conversely, whenever the physician secures a positive tuberculin reaction in a routine examination of a child, he should assume that someone in intimate contact with the child is a spreader of tubercle bacilli, and it is his duty to examine or have examined all suspects for tuberculosis.

Thus briefly may the whole problem of tuberculosis control be stated, but in between lies a voluminous plexity of questions, the answers to which, in some instances, are clear but in many others are still shrouded in obscurity.

The material for this review may conveniently be grouped under the following subjects: (1) résumé of the outstanding concepts of tuberculosis in children which seem fairly well established; (2) important controversial questions; (3) studies of a clinical nature; (4) extrapulmonary lesions; (5) further studies in diagnostic aids; (6) new concepts in case finding methods; (7) prevention and treatment.

RÉSUMÉ

To restate the significant points in the types of tuberculosis seen in children, reference is had to the excellent article of Allison and Medelman,[18] who base their observations on roentgenograms of 10,000 children seen at Lymanhurst and a large number at Glen Lake Sanatorium, who have been x-rayed at least once by stereoscopic films and many of whom have been studied repeatedly by x-ray. The classification of first infection tuberculosis as given by these authors is as follows:

A. Known infection with no demonstrable lesion.

Over half the children with positive tuberculin tests fall in this group. The primary focus may be in the abdominal or cervical lymph nodes, may be obscured by other structures in the chest, or may be so small as to be undemonstrable roentgenologically. As pointed out by Stewart,[19] these children are allergic to tuberculin and differ in no way from the children with primary demonstrable foci so far as their tuberculosis experience goes.

B. Uncalcified tuberculosis of the primary pulmonary or childhood type.

In this group are placed the children with primary parenchymal resolving or receding lesions and those with uncalcified tuberculous tracheobronchial lymph nodes. The primary focus or foci may be small or develop collateral inflammation amounting to consolidation of a whole lobe. To be differentiated are the progressive destructive lesions, acute pneumonias, bronchiectasis, atelectasis as from a foreign body, and the adult type of tuberculosis. Gradual resolution with deposition of calcium or a remaining fibrous strand makes the diagnosis certain. Uncalcified tracheobronchial gland tuberculosis can only be diagnosed roentgenologically when the enlarged node extends outside the hilus area. Resolution by calcification confirms the diagnosis.

Only 4 or 5 per cent of positive reactors from infancy to adolescence will show these types of lesions.

C. Calcified tuberculosis of the primary pulmonary or childhood type.

This group consists of those children who show calcification either in the lungs or in the lymph nodes or both. Such children have undergone the resolving lesions of Group B, and have developed stable lesions. It should be borne in mind, however, that calcification and caseation may exist in the same focus and that only the pathologist can tell whether or not a lesion is completely healed.

D. Adult type tuberculosis with or without demonstrable primary focus.

At least 50 per cent of all children with adult type tuberculosis have it superimposed on a demonstrable childhood tuberculosis.

In this classification the authors would place the rapidly fatal forms of tuberculosis such as miliary, bronchopneumonic, and meningeal, and the extrapulmonary lesions of bones, joints, and other viscera, in Group B. These, they feel, result from the breaking down of the primary focus with resultant dissemination of bacilli and happen in those cases in which the primary infection was massive. Myers,[20] on the other hand, prefers to classify such "complications" as reinfection types and would include them in Group D. This point will be considered further in subsequent paragraphs.

First infection tuberculosis is a benign disease. Most children are unaware they have it and do not know when they got it. Symptoms and physical findings are absent or very meager except in the few who develop extensive parenchymal resolving lesions, and these become symptom-free with the establishment of calcification. However, infants and children do die from tuberculosis, but compared to the number who are infected and survive the number of fatalities is surprisingly small.

It is the reinfection type of tuberculosis that is serious. Practically all infants and children will recover from a single primary infection, but when organisms gain entrance to the blood stream or to a bronchus from a caseous node or primary focus, they are disseminated to fall on allergic soil where quite a different reaction is set up than occurred with the original seeding. In infancy when opportunity for repeated massive exogenous reinfection is obviously greater than in older children, one might expect to, and does, see more frequent occurrences of serious reinfection types of tuberculosis. Considered from this point of view, there are two serious types of reinfection tuberculosis. The acute or rapidly fatal forms like miliary, progressive caseous pneumonia, and meningitis, and the less fatal but still serious bone, joint, peritoneal, kidney, and other visceral lesions comprise the first type, and are usually seen in the age group referred to above. The other killing type of tuberculosis, or phthisis, is of a more chronic character and is seldom seen in children before the age of eight or ten. By x-ray examination it can be recognized as a subapical infiltration sometimes three or four years before the development of clinical symptoms. The recognition of phthisis in this stage constitutes early diagnosis. What was formerly called early diagnosis, based upon positive physical findings and symptoms, was in reality very late diagnosis.

Whatever is one's belief in regard to the origin of these serious forms of tuberculosis, whether from an unstable primary focus and massive infection, or from reinfection on allergic soil, there can be no question but that the outstanding factor of paramount importance in the prevention of such serious illnesses is the prevention or interruption of contact with spreaders of tubercle bacilli.

CONTROVERSIAL QUESTIONS

Without doubt the most controversial question that has arisen out of the newer concepts of tuberculosis in children centers around the significance of a primary infection. The old idea was that everyone by the age of adult life had a little tuberculosis in him and that it was a good thing in that it gave him a certain degree of protection or immunity. Physicians were in the habit of telling parents of otherwise healthy children with positive tuberculin reactions that such a reaction was beneficial and that such a child was better off than his nonreacting playmate. But serious doubt has been cast upon this point of view particularly by Myers and Stewart in their publications from Lymanhurst which are based upon the follow-up study of more than 10,000 children over a period of eleven years.

These authors feel that a first infection type of tuberculosis is decidedly detrimental in that it hypersensitizes the tissues to tuberculoprotein and thus paves the way for the development of the serious reinfection forms of tuberculosis, which are serious because of the allergic state of the individual. They contend that a positive tuberculin test is

a liability, not an asset, and that from out of the group of children with the positive tests is going to come the crop of "consumptives" of tomorrow.

Myers[16] says: "We have come to the conclusion that producing the first infection type of tuberculosis in the bodies of infants, children, or adults, may be likened to the placing of bombs in their bodies. How these bombs are timed or how and when the fuses are lighted cannot yet be determined. Some may be timed for a few months; others for one hundred years or more; and still others for any intervening time." He goes on to cite cases at various age levels, from an infant five months old to adults fifty-six years old, whose roentgenograms show first infection and reinfection types of tuberculosis existing side by side. He concludes: "The first infection type of tuberculosis is a benign condition, with lesions which vary in size and number and which may at any time liberate bacilli into the blood stream or upon allergic tissues, which result in rapidly progressive miliary tuberculosis or chronic disease of the lungs, bones and joints, or other parts of the body. Such immunity as the first infection type confers is not complete in character. While it may tend to influence the chronicity of the infection, this is of slight value in view of the fact that the reinfection type cannot develop except on a basis of first infection type, and in a certain percentage of these reinfection cases, the disease progresses so as to result in illness and even fatal termination. In view of the accumulating data to the contrary, we are no longer justified in speaking of tuberculous infection without disease, for they are one and the same thing. These facts face us squarely with the proposition that control of tuberculosis means prevention. A satisfactory immunizing agent is not an actuality; prevention is. Employment of epidemiologic measures holds the same promise for tuberculosis as it does for other communicable diseases."

Stewart[19] studied eighty-four cases of "consumption" occurring in Lymanhurst children and came to the conclusion, ". . . primary tuberculous infections are distinctly detrimental in that they alter the normal resistance to tuberculosis present in the uncontaminated human body in such a manner that instead of again being able to experience the benign primary type of tuberculosis, the patient is doomed thereafter to develop consumption if successfully reinfected from exogenous or endogenous sources. The only method by which consumption can be prevented is through the prevention of tuberculous infections."

On the other side of the argument, Park, Kereszturi, and Mishulow[21] say, "This point of view (Stewart's), if true, has an important bearing not only on our present attitude toward arrested tuberculous infections but also on the desirability of producing an artificial allergy to tuberculin by means of attenuated vaccines like the B. C. G. vaccine of Calmette. Our aim by this form of attempted immunization is to give to the child who is believed to be not yet infected, or, at least, not seriously so, as shown by a negative reaction to tuberculin, his first tuberculous infection in a safe, well-calculated way.

"This vaccination depends on a belief exactly the reverse of the thesis of Stewart. We assume that hypersensitiveness to tuberculin and relative immunity to tuberculous infection usually develop together, and also that resistance to reinfection may outlast hypersensitiveness to tuberculin."

These authors have the feeling that massiveness of the infecting dose or doses is the determining factor in the development of serious forms of tuberculosis, and they express no surprise that Stewart's eighty-four children had phthisis since 81 per cent of them "had interfamilial exposure, which naturally renders them a highly endangered and highly selected group."

Furthermore, they point out that in 224 parenterally vaccinated children, 85 per cent of whom showed, at some time, a positive tuberculin reaction, there were no deaths from tuberculosis; whereas in 272 orally vaccinated children, in whom the occurrence of a positive reaction was much more rare, they observed three deaths from tuberculosis. If this difference in mortality rate is found to persist, under certain conditions, they feel it can be considered as contradictory evidence to Stewart's belief.

CLINICAL STUDIES

In Study II Reichle[22] presents clinical and roentgenologic evidence, based upon observations of 190 tuberculous children, in support of his contention in Study I that "... extensive exudates do resolve completely, and second, that it is impossible to differentiate from the mode of onset and the physical signs whether a given lesion will result in complete recovery or an extension of the disease process and death." He does not believe that there is any essential difference, anatomically speaking, between the resolving exudates and the progressive destructive lesions. Roentgenograms at any given time may be so similar as to make differentiation impossible. In the group of cases cited, in which the exudate eventually completely resolved, physical signs and symptoms were very evident; in several of them relapses were noted to occur both symptomatically and roentgenographically; in one case extensive pathology was produced by bronchiogenic spread from a supraclavicular gland, which subsequently cleared almost entirely. The author invites comparison of such cases as these with that of a colored girl, aged six years, in whom the issue proved fatal, but during six or seven months of observation there was nothing in this child's physical examination, symptomatology, or roentgenograms, to distinguish her from the children who resolved their exudates.

Reichle states it has been his experience "..... that the one essential difference between the resolving exudate and the frank caseous pneumonia is the course. The former improves when once it has reached its full bloom, whereas in the case of the latter the patient declines and passes into the cachectic stage, unless a complication, such as miliary tuberculosis, ends the course acutely."

Bronson, Zimmerman, and Powers[23] present a study of fourteen children, all but two of whom were under two years of age, from the point of view of correlating roentgenologic with clinical and postmortem findings. From experience they suggest the following roentgenographic technic as applied to tuberculous pathology within the thorax. 1. Roentgenograms should be taken with the chest in complete inspiration. 2. Routine roentgenograms of the chest should be taken at six-foot target—film distance. 3. Oblique views of the chest are important for the diagnosis of involvement of the mediastinal region. 4. In order to bring out calcium deposits clearly, it is important that films be not underexposed. 5. When possible, roentgenograms should be taken at various times during the course of the disease.

The authors point out that the value of such a study lies in the possibility of more correct anatomic and etiologic diagnosis from roentgenograms alone. Correct interpretation of shadows in the x-ray film indicative of tuberculous disease is not always easy. Calcium deposits and cavity formations can be interpreted as tuberculous processes in the vast majority of instances.

Dunham[24] made an important contribution to the literature in her report of seven infants, all under two years of age, all with pulmonary tuberculosis, and all of whom had been followed for a period of four years or more. The results of this study show that at the present time four of these children are considered well; two are still under treatment for tuberculosis; and one has died of tuberculous meningitis.

These findings are in keeping with the recently expressed opinion of several authors that tuberculosis in infants is not nearly so fatal as it was once supposed to be.

Doubt that epituberculosis is a pathologic entity is expressed by Morlock and Pinchin,[25] who cite the case of a fourteen-year-old boy presenting the roentgenologic picture of this condition. Bronchoscopy revealed a tumor obstructing the right upper main bronchus, the removal of which resulted in a clearing of the lung shadow in four days. The tumor proved to be a tuberculous lymph gland which was causing bronchial obstruction and atelectasis.

Such a possibility must, of course, always be kept in mind, but it seems very doubtful if the increasing number of reports of resolving parenchymal lesions corresponding to those reported by Eliasberg and Neuland can all be due to atelectasis.

Sanes and Kenny[26] describe an unusual tuberculous lesion occurring in the lung of a ten-month-old negro child. Postmortem examination revealed that the lower lobe of the right lung was distended and tympanitic. On section a large cavity was found "replacing almost the entire right lower lobe with apparently complete disappearance of pulmonary parenchyma. The cavity was bilocular. The largest part in the anterolateral portion measured 5.5 cm. in lateral diameter, and 7.5 cm. in frontal diameter; the smaller part in posteromedial portion measured 1×1.4 cm. The lumen was filled with 'air' and contained caseous material. Stretching across it were numerous small and large tubular and bandlike structures corresponding to bronchi and vessels." Air apparently entered the cavity but was unable to escape.

The authors feel that this "high tension cavity" formed about the primary pulmonary focus. The question might be raised, however, as to whether such a lesion is not more likely to have resulted from endogenous reinfection, bronchiogenic dissemination, and caseous pneumonia.

At the Undercliff Sanatorium, in Connecticut, Gibson[27] found nineteen children out of 200 current admissions with calcified abdominal lymph nodes as revealed roentgenographically. Goldstein and Wood,[28] in a study of seventy-one cases of phlyctenular conjunctivitis, searching for a tuberculous focus, found eighteen out of forty-eight positive roentgenograms in New Haven. From no other part of this country, so far as the reviewer is aware, has there been reported anything like these findings from New Haven and its vicinity. The explanation may lie in the failure of others to look for them roentgenologically as carefully as the New Haven workers do. One wonders if the incidence of

bovine tuberculosis and the consuming of raw milk is higher in Connecticut, since Woodhead[30] found tuberculosis in the mesenteric lymph nodes in 78 per cent of children in Edinburgh, where extensive bovine tuberculosis is known to exist.

Not only is this type of lesion important as the possible source of a positive tuberculin test, but also it not infrequently enters into the differential diagnosis of acute abdominal conditions, as Gibson points out. This author also stresses the importance of repeated abdominal roentgenograms in order that later deposition of calcium may not be overlooked.

Katzeff[31] conducted a statistical study to determine the numerical relation between orthopedic and nonorthopedic forms of tuberculosis admitted to the Children's Hospital of Boston between the years of 1884 and 1930, inclusive.

In 1891 the incidence of nonorthopedic forms was at its lowest point—27 per cent of the total tuberculosis cases. A gradual reversal of these figures took place until in 1930 the incidence of the nonorthopedic forms reached its highest level at 77.7 per cent.

The author concludes that this study confirms the impression "that tuberculosis of the osseous system is a disappearing disease and that this form of tuberculosis responds more favorably than the nonorthopedic forms to the measures of preventive medicine."

Greengard and Abrams[32] record the occurrence of spontaneous tuberculous pneumothorax in two infants observed by them. They point out the relative rarity of this condition in childhood as compared to adult life. "The symptomatology manifested by these two infants differed from that commonly observed in adults, in whom an abrupt onset with evidence of acute circulatory embarrassment and collapse is the rule. In these cases observed, the onset was insidious, and the presence of air in the pleural space was found on routine physical and x-ray examination. From a prognostic point of view tuberculous pneumothorax in infancy is to be looked upon as a manifestation of a malignant type of infection." Both of these infants died.

EXTRAPULMONARY LESIONS

Rich and McCordock[33] have published a report on the pathogenesis of tuberculous meningitis which disproves our previously held idea that this disease was the result of a direct hematogenous spread of bacilli, usually from a focus in the lung or tracheobronchial lymph nodes. I quote their summary: "Experimental and morphologic evidence is presented which demonstrates that diffuse tuberculous meningitis is not a direct and immediate result of hematogenous infection of the meninges. Miliary tuberculosis produces only rare, sparsely scattered tubercles in the meninges, not diffuse meningitis. Tuberculous meningitis has its origin in the discharge of bacilli into the cerebrospinal fluid from adjacent, older caseous tuberculous foci. Such discharging foci have been found, by careful search, in the substance of the brain or cord, in the meninges, in the bones encasing the central nervous system, or in the choroid plexus in seventy-seven of the eighty-two cases of meningitis in our series. In all except two of these seventy-seven cases the demonstrated source of the diffuse meningitis was situated in the substance of the central nervous system or in the meninges. In the five cases in which no local focus was found, the material for study was incomplete."

That phlyctenular conjunctivitis is frequently of tuberculous origin has been established for some time. Goldstein and Wood,[28] however, in a splendid presentation, show how close this relationship may be demonstrated to be when a thorough search for tuberculosis foci is made with modern diagnostic procedures. Of seventy-one children with phlyctenulosis, forty-eight, or 67.6 per cent, gave positive roentgenologic evidence of tuberculosis. In eighteen of these forty-eight, the focus was demonstrated in the abdominal or cervical lymph nodes. Thirteen of the children had suggestive roentgenograms while only ten gave negative films. Tuberculin tests were positive in fifty-eight out of sixty children tested. In one of the two negatives a von Pirquet test only was made, and in the other the phlyctenulosis was atypical in that it lasted only three days.

In recent years the literature contains an increasing number of investigations purporting to establish the etiologic agent in erythema nodosum.

There are at present adherents of at least three views, concerning the cause of this disturbance. The first, the rheumatic, has long been held to be the correct interpretation, but dissenters point out the infrequent association of erythema nodosum with chorea and endocarditis as evidence against such a belief. Second, the stand is taken by some that erythema nodosum is an acute specific disease. Moon and Strauss,[34] for instance, isolated an organism from the lesion of each of two cases of erythema nodosum, which, when inoculated into animals, reproduced the lesion. They suggest the organism isolated be designated by the term "*Corynebacterium cutis nodosae.*"

But by far the most convincing evidence has been brought forth by the advocates of the third view—the tuberculous agent.

Wallgren[35] believes that erythema nodosum occurs at the time of greatest activity in the hilar nodes directly following their involvement from the primary focus. At this time he feels the primary pulmonary lesion should still be open, and in proof of his contention he demonstrated tubercle bacilli in the gastric contents of seventeen out of forty children with erythema nodosum, all but three of whom were positive to tuberculin. The roentgenograms of these children showed only more or less enlarged hilar shadows. The author feels he has shown conclusively that children with positive tuberculin tests, and enlarged hilar shadows, really have tuberculosis, and that "this ought to be regarded as an argument in favor of the tuberculous nature of the erythema." Another interesting fact brought out by this study was that in this group of children with typical childhood tuberculosis the tendency was for the stomach contents to become negative after a few months. This has an important bearing upon the possible duration of transmissibility of first infection types of tuberculosis.

Dickey[36] studied sixteen cases of erythema nodosum in children and found a positive tuberculin reaction in all of them. In ten a definite perifocal reaction was demonstrated roentgenologically, and in an additional case the focus was in the cervical lymph nodes.

In a series of thirty-three pupil nurses who had had erythema nodosum, Cruise[37] states that one-third either developed definite tuberculosis or were suspected of tuberculosis at the time of the rash or within six months, in all but one instance. Over half of the nurses developed the erythema at the time or shortly after service on a tuberculosis ward.

Collis[38] contends that "erythema nodosum is a hyperactive tissue response to different bacterial allergens, and that the allergens responsible for the disease in London are commonly tuberculin and hemolytic streptococcal endotoxin." In an earlier report of eight cases of erythema nodosum, five reacted only to tuberculin, and three only to streptococcal toxin (rheumatic). In the present study thirty-eight additional patients with erythema nodosum were studied in London and eleven in Dublin. Of the London group 71 per cent were of tuberculous origin, and of the Dublin group 90.9 per cent. In London 18.4 per cent of the cases were classified as rheumatic, and only 9.1 per cent in the Dublin. In the London group 10.6 per cent were indefinite.

The author feels that while erythema nodosum may be brought about by more than one allergin, by far the commonest is tuberculous infection, and that it should be our attitude to regard every case as tuberculous until proved otherwise.

DIAGNOSTIC METHODS

With advancement in knowledge of tuberculosis in children, tuberculin testing has taken a place in the front rank of diagnostic procedures. The specificity of the allergic reaction is unquestioned. Investigators are chiefly concerned in finding a method of applying the test that is simple and painless, and yet which retains a high degree of accuracy, in the development of a purified tuberculotoxin, and in the study of variations in the size of the reacting area in relation to the disease process.

Grozin[39] has introduced the "tuberculin patch test" into this country. This test consists in simply placing a drop or two of Koch's old tuberculin on a piece of adhesive tape 3×3 cm. and applying this to an area of skin. At the end of forty-eight hours the tape is removed and the test read. The author finds it to have 96 per cent agreement with the von Pirquet test.

A similar test is that described by Wolff,[40] who has devised an ointment containing a highly concentrated tuberculin and killed tubercle bacilli. A pea-sized drop of the ointment is applied to the skin of the back between the eighth and eleventh vertebrae and covered with a 2-inch adhesive tape. A positive reaction exhibits papules, erythema, induration, and pigmentation at the end of forty-eight hours. In 190 children the percentage of agreement between the ointment and the Mantoux test using 0.1 mg., 1.0 mg., and 10.0 mg. O.T., was 95.8 per cent.

Greengard and Nichamin[41] conducted an experiment to determine the relative merits of a purified protein tuberculin (T.P.T. Seibert); a tuberculin ointment devised by Lowenstein designated as dermotubin; the Mantoux test using 0.1 mg. O.T.; and the von Pirquet test. These tests were run simultaneously on 647 consecutive children admitted to Cook County Children's Hospital. A total of 185, or 28.6 per cent, positive tests were secured. Of these 178, or 96.2 per cent, came from the T.P.T.; 166, or 89.7 per cent, from the O.T.; 152 or 82.1 per cent, from the dermotubin; and 121, or 65.4 per cent, from the von Pirquet.

These authors express the conviction that the intracutaneous test should always be used as a routine in all children's hospitals, but that in office practice the dermotubin has much to recommend it.

Further investigations of the type indicated by these three studies seem desirable. Practically everyone is in agreement that the intracutaneous is the most accurate of all the tests and ought to be used by everyone in the interest of securing comparable data. However, there can be no question but that the technical difficulties of preparation and administration enormously retard its use by the rank and file of physicians. If a test as simple as the patch or ointment tests described above can be devised that will equal the intracutaneous method in accuracy, a great increase in the use of this valuable diagnostic procedure can be anticipated.

Numerous research studies are being carried on with various forms of purified tuberculoprotein in search of a pure substance suitable for tuberculin testing in human beings. The best known of these are MA-100 and T.P.T. (Seibert). The former is the fraction precipitated by ammonium sulphate, whereas the latter is precipitated by trichloracetic acid. Apparently both possess the ability to sensitize after repeated injections, thus giving rise to false reactions (Arthus reaction), while old tuberculin does not bring about a hypersensitive state.

Aronson and Nicholas[42] conducted tests on human beings with O.T. (Dorset) and tuberculoprotein (MA-100). Of 281 persons tested, 14.7 per cent reacted to the first dose of 1.0 mg. O.T., and 9.7 per cent reacted to the first dose of 0.05 mg. of tuberculoprotein. Of 94 persons retested, only 7.4 per cent reacted to 1.0 mg. of O.T., whereas 31.1 per cent reacted to 0.05 mg. of tuberculoprotein (MA-100).

Seibert[43] describes her efforts to isolate a tuberculoprotein of different molecular weight which would be free from sensitizing properties.

The degree of skin sensitivity as measured by the tuberculin test in relation to the extent of demonstrable intrathoracic pathology of first infection type has been investigated by Stewart.[44] Contrary to what many of us feel should be the case when we observe an extensive reaction, he states, "This study on living patients failed to disclose evidence that justifies one in entertaining suspicions that children with large and intense Mantoux reactions harbor more extensive pathologic changes or have more active primary tuberculous lesions than do other children who are less sensitive to tuberculin."

An interesting study of the tuberculin reaction was contributed by Johnston, Howard, and Maroney.[45] These authors determined the least amount of tuberculin necessary to produce a reaction throughout the evolution of a primary complex. Doses as small as 0.000,000,01 mg. O.T. were used. There was a gradual rise in hypersensitivity which reached a "high peak following the absorption of the parenchymal lesion and corresponding with the maximal involvement of the hilum lymph nodes, and then a decline with the diminution in size of these nodes and their calcification." The time interval for the period of increase was from three to eight months, and the period of maintenance of the high plateau was an additional several months.

Stewart[46] investigated the growth of the reacting area to 0.1 and 0.01 mg. O.T. at 3-, 24-, 48-, 72-, and 96-hour intervals after applying the test to 160 children. The area of the reaction was determined by outlining it in ink, superimposing a special transparent celluloid composition which was over-traced, cut out, and weighed. Dividing this weight by the weight of a portion of the same paper, the area of which

was 1 sq. cm., gave the area in square centimeters of the reaction. Stewart found that the average maximum area to 0.1 mg. O.T. was 30.2 sq. cm. although there was tremendous individual variation. (In another study[47] maximum individual areas varied from 0.33 to 161.29 sq. cm. in size.)

Maximum growth of the reacting area was reached in twenty-four hours in the children who were slightly or moderately hypersensitive to tuberculin and in forty-eight hours in the children more highly allergic. The area of the cutaneous reaction to tuberculin is not directly proportional to the amount of tuberculin used. The ratios of areas of reactions obtained are found to be approximately three to one when the doses of tuberculin used are ten to one (0.1 mg. and 0.01 mg., respectively).

Examination of gastric contents of children for tubercle bacilli has been reported from time to time since the method was first described by Maunier in 1898. Especial interest, however, has developed in the procedure in recent years not only in connection with its diagnostic possibilities, but more particularly in connection with the bearing it may have upon the question of infectivity of children who show evidences of the first infection type of tuberculosis only.

Friedman, Esserman, and Black[48] inoculated homogenized stomach washings into guinea pigs from each of sixty children. Two of these gave positive results. Each of these two children gave a history of contact with the tuberculous, was a reactor to tuberculin, had only questionable radiographic evidence of nodular type of infection, and was free from cough, expectoration, fever, and tendency to colds.

Collis and Brockington,[49] using the same technic, secured twelve positive results out of seventy children investigated. One of these was a contact child who showed no evidence of tuberculosis.

Gourley[50] studied fifty-nine cases of childhood tuberculosis by gastric lavage and guinea pig inoculation. Fifty of the fifty-nine had demonstrable lesions in the roentgenograms of the lungs. Nine had no demonstrable lesions. These nine had negative gastric contents. Of the fifty with demonstrable lesions, twenty-eight had positive gastric contents. Five of the twenty-eight had only calcium in the parenchyma of the lungs or regional lymph nodes.

Kereszturi, Hauptman, Schick, and Mishulow[51] report a series of 101 tuberculous children representing different forms of tuberculosis, some of the patients showing nothing but a positive tuberculin test, others far advanced bilateral destructive lesions, of whom 27.7 per cent gave positive results for tubercle bacilli in the stomach content. If guinea pigs were not used, the smear examination of stools yielded only 7 per cent less positive results than the more cumbersome stomach lavage. Sputum and throat-swab examinations gave positive results less frequently than did stool or stomach-lavage examinations. In this group of cases the finding of tubercle bacilli in the stomach contents was of grave prognostic significance. Clinically inactive cases gave only negative results.

Somewhat different are the findings of Nalbant[52] who, in a group of sixty-five tuberculous children, found twenty-four who gave positive results for tubercle bacilli in the feces or sputum. Seven of the positive results came from among nineteen children who showed no signs of pulmonary disease. The remaining seventeen positives were from children who had demonstrable parenchymal infiltrations of the childhood

type. Nalbant also feels that repeated examination of stools will yield as high a percentage of positives as gastric lavage, and with a great deal more comfort to the patient.

The results of such studies as these immediately raises two pertinent questions. What is the source of the tubercle bacilli in the gastro-intestinal tracts of children showing no signs of pulmonary disease, and are children with first infection type of tuberculosis possible spreaders of tubercle bacilli among their playmates?

Four years' experience with examination of material obtained by gastric lavage have enabled Paulsen and Andersen[53] to supply answers to these questions. In all, these authors have examined 622 children, 199 of whom have shown tubercle bacilli in the stomach contents. A marked relationship between positive findings and age of the patient has been demonstrated. Sixty-two children were examined during the first year of life, and bacilli were demonstrated in fifty-four of these. In the second year of life bacilli were demonstrated in about one-half of the patients examined; in the third year, in about one-third; and in the fourth year, in about one-fifth. Three examinations yielded a higher percentage of positive results than one or two, but no greater than four or five. Wallgren[35] has shown that there is a tendency for the stomach contents to become negative in six or eight months, indicating that this is the length of time required for closing of the primary focus. Lester[54] has demonstrated the viruleney of the acid-fast organisms obtained by gastric lavage to be the same as tubercle bacilli obtained from other sources. She also found fewer colonies of tubercle bacilli in the stomach contents of children under ten years of age than in those over ten and in adults.

On the basis of these findings, and concerning only children with the childhood type of tuberculosis, it seems reasonable to conclude that the source of tubercle bacilli, if faucial disease be excluded, is the primary pulmonary focus; that these bacilli are virulent; and that there is a real danger to healthy children, for a time at least, from such infected children, particularly those under four years of age.

CASE-FINDING METHODS

A study of the literature of the past year indicates that investigators are seeking to determine the method or methods of conducting case-finding programs that will yield the most satisfactory results at the lowest per unit cost.

The National Tuberculosis Association[55] has published a third brochure entitled "Procedure for the Discovery and Care of Tuberculous Children." It constitutes a summary of the measures which have proved to be most successful up to the present time. The brochure states, "The simplest and most satisfactory plan for discovering tuberculosis among children seems to be to make tuberculin tests of all children of a given group and to examine all positive reactors with the x-ray."

What groups should be selected?

Korns'[56] conclusions after a study in a rural county in New York state are as follows:

1. More tuberculous infection and disease were found by examining contacts of diagnosed cases than by examining routinely apparently healthy school children.

2. Tuberculin testing of large numbers of elementary rural school children is time consuming and expensive. The infrequency of tuberculosis in this group of children would hardly warrant the use of this method in Cattaraugus County.

3. Tuberculin testing of high school students is desirable in the hope that, by x-raying the reactors, adult lesions may be discovered before illness causes the student to seek medical advice.

Bridge and Stokes[57] compared results obtained when children were examined in the dispensary and in the schools in a rural part of New York state. They found four times as much tuberculosis among contacts and below par children as they did among healthy rural school children, and ten times as many cases of childhood diffuse and adult type of tuberculosis.

These studies suggest therefore that in those sections of the country where the incidence of tuberculous infection is low, case-finding programs will yield the greatest results if confined to the contact group and the high school group of children.

A recent development of great promise for the examination of large numbers of individuals is the Powers x-ray paper in rolls. By means of this film and a specially designed camera as many as 150 x-ray exposures an hour can be made, and the rate maintained. The film is developed in roll form, and the pictures are read in roll form in a specially designed viewing cabinet.

Edwards[58] reports in detail the conducting of a case-finding program in New Haven using this apparatus, and omitting previous tuberculin testing. A total of 6,502 pictures were taken in ten and one-half days. About 200 to 250 could be read in an average day. Only those pupils who agreed to pay sixty cents were x-rayed. The Powers equipment is rented, and technicians are furnished with the rental price. In this instance the rental fee was sixty cents per film. New expenditure by the Department of Health amounted to only $137.25.

Edwards concludes, "The unit cost incurred in case finding among 6,393 individuals in New Haven was reduced 50 per cent over the preselection tuberculin method by using Powers' x-ray paper in rolls. The x-rays were of remarkable uniformity and equal in quality to celluloid. This method of detecting latent and manifest lesions among pupils in their teens, in our experience, is superior to the preselection by tuberculin method."

Barnard[59] used the same method in examining 20,000 individuals in New York City and concluded, "It would not have been possible by any other method to have so quickly and easily surveyed this large number of individuals and selected those needing care."

In both of these studies the disposition of the individuals with positive chest findings was always back to the private physician. This brings up the point as to the part the private physician is to play in the tuberculosis case-finding programs of the future. Quite properly health departments and tuberculosis workers have taken the lead in the preliminary experimental investigations, but, if best results are to be achieved in the future, there ought to be the closest cooperation with organized medicine and the private practitioner. Already there are several precedents established indicating how this may be done, the success of which may well serve as a guide to other communities.

In Detroit[55] the Health Department has extended its well-known plan for diphtheria prevention to include case-finding work among children. Under this plan the private physician does the actual work of tuberculin testing, x-raying, and examining.

Baker[60] discusses the problem of tuberculosis control in the South and outlines the procedure now in force in Alabama. The county serves as the unit of operation, and the tuberculous family as the main point of concentration.

In Texas the State Tuberculosis Association is apparently the active agency in promoting this type of work. Wright[61] states that the prophecy made last year, "The time will come when every school child in Texas will be skin tested for tuberculosis," will likely be fulfilled in a few years.

PREVENTION AND TREATMENT

Two objections have been raised to the use of B. C. G. The first is that under certain conditions the culture may regain its virulency and produce progressive tuberculosis in the inoculated individual; and the second is that the allergy produced, like the allergy following first infection, may be detrimental in that it paves the way for the development of the more serious reinfection forms of tuberculosis.

Calmette[62] states that more than a million children have now been vaccinated the world over, and "not a single clinician or pathologist in the world has been able to prove that one could isolate virulent B. C. G. from the organs of a child vaccinated with B. C. G. and who died some time afterward."

He considers the claims of those who have experimentally restored the virulence of B. C. G., and emphatically refutes their findings by citing numerous other workers who have been unable to reproduce such claims.

Birkhaug[63] reports the results of a three-year study and concludes, "B. C. G. is harmless as a vaccine and is capable of arousing an outstanding and significant tuberculoimmunity when administered to guinea pigs by the parenteral routes."

Park[21] and his coworkers were also unable to increase the virulence of B. C. G. under the special methods of cultivation and inoculation utilized by those who believed they had seen an increase in virulence.

Whether or not the allergy produced in human beings by inoculations of B. C. G. is harmful or beneficial is a disputed point, the answer to which will have to be determined by further study and observation.

Finally, there remains to be considered the prevailing views as to what constitutes adequate care for children afflicted with various forms of pulmonary tuberculosis. Of particular interest in this regard are the group of children harboring first infection type of tuberculosis only and the much smaller group who have developed the reinfection type, or phthisis. Concerning the former group, Myers[64] states that their views at Lymanhurst have undergone a radical change in recent years. Whereas they formerly believed that any tuberculous inflammatory process visible in the roentgenogram indicated a need for strict bed rest in a sanatorium or at home, they have now come to realize, through observation and experience, that such lesions undergo resolution and healing equally well without any special form of treatment, or at least only such treatment as constitutes any well-regulated health program.

"Our observations on these children have convinced us that the use of their homes, foster homes when necessary, the family physician, clinics for the needy, the school system, and nursing and social organizations is the best solution of the treatment and protection of such children. The individual's home is surpassed by no other place when the source of exposure is discontinued and the other home conditions are good. . . . The Lymanhurst medical staff is strongly of the opinion that sanatoriums and twenty-four-hour preventoriums are usually unnecessary in the treatment of children with first infection type of tuberculosis."

Hawes,[17] on the other hand, from his experience with the Prendergast Preventorium in Boston, is strongly of the belief that such institutions are well worth the investment in time and money. Outside activities by the preventorium staff in the homes of the "contact" children he considers as particularly valuable. Also the preventorium provides a place for the instruction and training of these infected children so that when they return to their homes their chances of continuing in good health are greatly increased. The Prendergast Preventorium cared for 899 "contact" children in the ten-year period from 1922 to 1932. Of this number there has since been only one death from pulmonary tuberculosis, and only two children have developed the disease since discharge. One hundred and nine children have been returned to homes where the source of tuberculosis has not been eliminated but apparently have progressed as well as the others, which fact Hawes believes attests the value of the training and education given by the preventorium workers.

Desirable as preventorium supervision may be for children with first infection tuberculosis, the lack of availability of such institutions to the majority of private practitioners places the responsibility for adequate care of these children squarely upon the shoulders of the physician. What constitutes adequate care may be assumed to be the measures which the preventorium, or its equivalent, has found to be successful. As has been pointed out elsewhere the all-important objective is the prevention of the development of serious reinfection tuberculosis. The physician's responsibility then, to the patients of this type occurring in his practice, consists in securing an environment free from virulent tubercle bacilli, maintenance of what is ordinarily understood to be an adequate health program for a normal child and sufficiently frequent physical and x-ray examinations to determine the course of the tuberculous process.

Crimm, Raphael, and Schmute[65] added a special cereal mixture to the diet of tuberculous children and secured an increased gain in weight and in hemoglobin over a control group. They concluded that the vitamin B content of the cereal was responsible for the gain in weight and the mineral content for the gain in hemoglobin. The results were not so good when vitamin B concentrate or minerals were added to the regular diet as were secured with the special cereal.

An interesting study with a possible bearing upon the treatment of tuberculosis in the human being is reported by De Savitsch, Trevorrow, Black, and Lewis.[66] These authors administered viosterol and tuberculin to guinea pigs rendered tuberculous and concluded, "The use of a combination of viosterol and tuberculin in the treatment of moderately advanced tuberculosis in guinea pigs gives definitely beneficial results, as judged by longevity, degree of tuberculous involvement, and amount of fibrosis."

The seriousness of the adult type of tuberculosis occurring in children is revealed by the reports of Morgan[67] and Pope.[68] Of 200 admissions of children with pulmonary tuberculosis from ten to seventeen years of age to the Westfield State Sanatorium from 1910 to 1920, 80 per cent are now known to be dead, and thirty-three individuals could not be traced. Of 195 admissions from 1920 to 1927, 68 per cent are dead with twenty-four individuals not traced. Forty-one per cent of the patients in whom the disease was classed as minimal in this group have succumbed.

Such statistics, which can be accepted as being fairly representative, bring out sharply the need for a more effective form of treatment for children with phthisis.

In recent years some form of collapse therapy seems to be meeting this need admirably. The use of tuberculin and x-ray examination has lent a new meaning to early diagnosis, so that artificial pneumothorax is now being administered to patients even before symptoms begin. In this regard Myers[69] says: "In the past, most cases of tuberculosis reached the moderately or far advanced stage before their disease was diagnosed or while under observation. In the occasional case seen while the disease was minimal, artificial pneumothorax was usually thought to be contraindicated. Therefore, very few reports on artificial pneumothorax work contain many cases treated in the minimal stage. However, with our modern diagnostic methods, a much larger number of cases are being detected while in the minimal stage. By the more extensive use of these methods, we may hope to arrive at a time when the majority of cases of clinical tuberculosis will be detected before symptoms make their appearance. Through observations made at the Lymanhurst School for Tuberculous Children, the University of Minnesota Health Service, and elsewhere, we have been convinced that every progressive case of minimal tuberculosis of the reinfection type should be treated by artificial pneumothorax."

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FOURTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

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Round Table Discussion on Allergy

Leader: Béla Schick, M.D., and Assistant, M. Murray Peshkin, M.D., New York, N. Y.

CHAIRMAN SCHICK.—The term "allergy" was coined by von Pirquet, who defined it as an altered reactivity of the body to the reintroduction of a pathogenic organism. The state of allergy embodies different features. Allergy occurs actually at the beginning of a disease if one is dealing with a bacteria producing a substance which is not toxic per se. In diphtheria there exists a short incubation period which permits the toxin (which is primarily toxic) to reach a certain concentration before a pathogenic effect is induced. A relatively longer incubation time occurs in measles, tuberculosis, syphilis, and other diseases because the invading germs are not primarily toxic. The body is not able to fight off this new invader immediately. Antibodies are formed under the influence of the pathogenic substance. These antibodies either kill the invading germ and liberate a toxic substance (endotoxin), or the bacterial substance itself becomes toxic only under the influence of these antibodies. The onset of the disease is determined by the appearance of these antibodies. Their presence indicates an allergic state. If reinfection or superinfection takes place, it is not necessary for the body to wait for the production of new antibodies for symptoms to develop. The host is capable of either reacting immediately or after a shorter incubation period. Therefore, we should recognize that allergy is a very widespread phenomenon and that almost every disease may possess allergic features. In the acute diseases we are capable of entirely killing off the germ or neutralizing its harmful effect. As a consequence of this, the disease quickly comes to an end. The state of chronicity occurs because of the inability on the part of the host to either destroy the germ or to neutralize its harmful effects.

The recent literature contains much discussion about the allergic nature of such a disease as rheumatic infection. This contention is nothing unusual or even striking for it is self-evident. If one speaks of allergic disease per se, then some other meaning is implied. This alludes to the condition of altered reactivity which may be accompanied by such intensive symptoms that an unpleasant and sometimes a dangerous situation occurs. Such an intense reaction is referred to as being an "hyperergic reaction." The hyperergic reaction is also referred to as anaphylactic shock. A person with asthma, eczema, or some other so-called "allergic disease" is recognized as suffering with an ergic reaction. Allergy really is not a good term for this condition because allergy may exist without hyperergic features.

Allergy is not harmful or dangerous, despite the statements made by Dr. Rich to the contrary. It is the hyperergic reaction that may become dangerous. The patient with asthma or eczema may be hyperergic to a minute amount of foreign substance. Some authors state the condition of allergy is not essential for immunity in tuberculosis. This contention is incorrect. It is the hyperergic reaction that is not necessary and in fact is even disadvantageous. Pirquet and I showed in our studies on serum sickness and Pirquet in his study on vaccination showed that the hyperergic reaction is something we do not need and is only an unpleasant accompaniment of allergy. In the case of a first infection with a vaccine, a minute amount of pathogenic virus invades the host. A relatively long incubation period is necessary to the formation of antibodies. The invading germ, meantime, multiplies while the antibodies are being formed in sufficient amount to fight off the invading virus. If the individual is in possession of antibodies or is capable of forming antibodies quickly, it is a great advantage. In contrast to this first infection bringing about this altered reactivity called "allergy," we take the instance where the person is reinfected or superinfected. In the latter instance the host reacts immediately. The invading virus is killed off immediately or at least very quickly, so that the amount of pathogenic organisms capable of reacting with the antibodies is very small; in fact, the number of pathogens reacting with the antibodies with the second or later invasions is very much smaller than in the case of the first invasion of the host. This type of allergic reaction in itself is good, but, unfortunately, allergic reactions as a result of overdosage of pathogens are sometimes accompanied by hyperergic reactions, and these latter reactions are harmful to the host.

So far as acute infectious diseases are concerned, hyperergic reactions are rare. In a chronic infectious disease such as tuberculosis, hyperergic reactions commonly occur. It should be emphasized that an hyperergic reaction represents only a small part of the entity referred to as the allergic reaction. Moreover, clinical immunity is based on allergy. Pirquet even favored the idea of considering antitoxic immunity as it occurs in diphtheria on a basis of allergy. Unfortunately, the hyperergic reaction is almost always identified only with allergy. In order to avoid confusion, the allergic diseases should really be called "hyperergic diseases." The confusion did not originate with the clinician but with the serologist who studied the anaphylactic (hyperergic) reaction in the guinea pig.

Hyperergic reactions occurring in infectious diseases are unpleasant and not desired. We may go further and say that the hyperergic reaction does not belong to immunity. Allergic reactions may bring about immunity but not the hyperergic reaction. We can separate immunity on the one side and hyperergic reaction on the other. Therefore, the treatment of tuberculosis with tuberculin may well be revived. The treatment with old tuberculin is nothing more than a process of desensitization. If some individual has a tuberculous focus, he may become hyperergic to tuberculin and making such an individual hyposensitive may do good.

Returning to the subject of asthma, it can be broadly stated that it is proper and desirable to institute measures which will diminish the sensitiveness of an hyperergic individual. The patient should be sufficiently cared for so that a severe (hyperergic) reaction is avoided when he comes in contact with the offending substance. If a person is sensitive to nuts, it is unwise to inject him with an extract of nuts, for it is much better and simpler to avoid them. It becomes necessary to desensitize (hyposensitize) a person suffering with hay fever when for economic reasons he is unable to migrate to a relatively pollen-free country. In Europe the wealthy people go to Helgoland where they are relieved of hay fever. However, the vast majority of persons with hay fever in Europe, as well as in the United States, cannot afford to spend some weeks in a pollen-free environment, and they are obliged to submit to hyposensitization treatment with specific pollen extracts.

Dr. Peshkin, who is chief of the clinic for allergic diseases in my department at the Mount Sinai Hospital, has worked out a routine for testing which we think is the most reliable and safest technic for children. The scratch method of testing is always done first, and, if the reactions are negative, then the intracutaneous or intradermal method of testing is performed. In the absence of positive reactions to the intradermal tests, especially with the pollens, then the ophthalmic technic is employed. It should be realized that there exists no absolute difference between the three methods of testing. It is merely a matter of concentration of the test material. If you perform a scratch test for tuberculosis, it is permissible to use the concentrated old tuberculin. If, however, you wish to test intracutaneously, then a dilution of tuberculin must be used.

It is true that different persons as well as the same person differ in their clinical response to specific hypersensitiveness. Because of this difference in reactivity the clinical manifestations of hyperergia may become localized in an tissue or organ in the body. If the brain is hyperergic, then migraine or epilepsy may develop. If the gastrointestinal tract is involved, vomiting, diarrhea, colic, and other symptoms appear. Hyperergia of the skin results in urticaria, lichen urticatus, and eczema. If the respiratory tract is the seat of hyperergic activity, symptoms of hay fever or asthma will be observed. Hyperergic reactivity may be present in more than one organ of the body. For example, asthma and eczema frequently occur in a child concurrently or at different times. There also exists some relationship between the different organs of the body. For instance, hypersensitiveness of the respiratory tract can usually be confirmed by means of the protein skin tests. In eczema and especially in urticaria, it must be conceded that the skin tests (scratch and intradermal technics) are not very satisfactory. Even the patch test frequently gives disappointing results. As a matter of fact, all methods of testing have their limitations. A negative test does not rule out the offending factor. Positive cutaneous reactions elicited by testing demonstrate only the hyperergic state of the skin. Positive reactions vary in their intensity. The importance of each positive reaction in the etiology of the hyperergic state must be determined individually. Peshkin has shown that (with the scratch test) a very mild reaction (one-plus or plus-minus) may play a more important rôle in the etiology of hyperergia than the positive reactions of greater intensity.

To begin with, many children have an inherent predisposition to hyperergic reactions, and hyperergic disease may be initiated as a result of various intercurrent conditions. During life the localization of the hyperergic reaction may change and shift. A child starts in infancy with eczema and within one to seven years it may develop asthma. If an infant is sensitive to certain substances with which it has never come in contact, then the work of Ratner regarding the question of sensitization through the placenta during embryonic life must be considered. It is also important to inquire into the diet of the pregnant woman. It is quite possible for the mother to sensitize the child during intrauterine life. All this is very interesting, but it complicates the subject.

From the standpoint of treatment it can be safely stated we do not cure but relieve asthma. The word "cure" cannot be applied to a condition in which the predisposition to that condition always remains with the patient. We treat the tendency to attacks either by avoiding the offending substances or by the process of hyposensitization. Nature sometimes also institutes her own treatment. Something is made to happen to the constitution of the child, and the tendency to hyperergic reactions is diminished.

Before closing my introductory remarks I wish to repeat that the state of allergy should not be considered harmful but rather a beneficial one. The hyperergic reaction is harmful. The hyperergic reaction may be harmful in tuberculosis. A recent

publication indicated it was dangerous to be primarily infected with tuberculosis and that it is much safer not to be infected. I do not believe that primary infection in tuberculosis, as such, is bad. It may be admitted that if some one is primarily infected with tuberculosis and is then exposed to a violent superinfection he is worse off than the person who was never infected. A violent infection is dangerous under all circumstances.

A person primarily infected with tuberculosis and highly hyperergic may also be damaged by this hyperergic state inasmuch as superinfection of mild degree may lead to an unnecessarily violent local reaction. But the majority of children previously infected with tuberculosis show a relatively low degree of hyperergic reactivity. The beneficial part of their allergy will outweigh the detrimental part of hyperergic reactivity.

Dr. Peshkin, after his talk on the practical side of allergy, will assist me in answering your questions. Do not expect us to answer every question to your entire satisfaction. Our knowledge on the subject of allergy is by no means complete.

DR. M. MURRAY PESHKIN.—The introduction of a practical method of determining by test the reactivity of the skin to various protein substances has been solely responsible for the considerable progress made in the study and care of children suffering from various allergic syndromes. The present-day conception of the exciting factors which cause asthma and allied conditions differs considerably from that of former years. Toward that newer conception a voluminous amount of literature has been contributed which has obtained a vast accumulation of valuable material. Many workers consider the present status of the subject of allergy almost a complete science. This attitude is largely responsible for some of the confusion that has crept into the subject. However, this state of affairs does not justify the attitude of some physicians of repute who still view the entire subject with unseasoned criticism and unwarranted skepticism. With an appreciation and regard for this controversial situation, it is safe to state that we can now impart enough practical information which will enable you to treat intelligently and appropriately allergic conditions of childhood.

The term "allergy" has been almost universally adopted to include those conditions exhibiting sensitization phenomena. Dr. Schick prefers to designate these conditions by the term "hyperergy." Other "synonyms" employed in this country are "atopy" and "human hypersensitiveness." Depending upon the location of the tissue or organ affected, the allergic syndromes known to be caused by specific sensitization are as follows: asthma, spasmodic bronchitis, croup, seasonal hay fever, vasomotor rhinitis, vernal conjunctivitis, serum sickness, eczema (contact dermatitis and neurodermite), pruritus, dermatitis venenata, urticaria, angioneurotic edema, migraine, mucous colitis, cyclic vomiting, enterospasm, and certain forms of epilepsy and purpura.

With such an array of conditions the physician cannot help but come to the realization that allergy assumes an important place in the study and care of childhood diseases.

The procedure employed in a search for the etiologic symptoms of an allergic affection involves a carefully taken, detailed history, protein skin tests, and a thorough physical examination employing necessary laboratory and other diagnostic aids.

HISTORY—TOLERANCE—HEREDITY

The importance of securing a proper history cannot be overemphasized. The history has a direct and significant bearing on the interpretation of the protein skin tests and other clinical findings. It often dictates the form of therapy to be instituted. It frequently tells you whether or not a positive skin reaction plays a rôle in the etiology of the allergic syndrome. It tells you that a patient can be

sensitive to material matter in spite of the fact that the skin test may be negative. The history also can act as a guide or a clue to a patient's tolerance.

Many workers regard the basis of allergy as a disturbed balance between the sympathetic and parasympathetic nervous system. A more logical conception of allergy would be that there exists within the body a physiochemic disturbance which probably manifests itself through the nervous system. Vaughan prefers to use the term "allergic imbalance." If the body is in a state of physiochemic equilibrium, the allergic patient enjoys freedom from symptoms in spite of exposure to an etiologic protein. Such a patient is said to have acquired a protein tolerance. Because the tolerance is so variable, allergic conditions, and especially asthma, are remittent and intermittent. Failure to appreciate that fluctuating variations of tolerance exist in different patients, as well as in the same patient, leads to misinterpretation of the rôle that protein sensitization plays in asthma. "Tolerance" is a term employed only in the language of the clinician. If any factor—specific or nonspecific or both—is allowed to overthrow the mechanism that governs a "balanced physiochemic state" symptoms will result.

About 10 per cent of so-called normal persons show positive skin reactions to test substances. The history indicates that these reactions do not enter into the etiology of any of the patient's complaints. These positive tests should not be regarded as mere accidents for experience has proved that such individuals must be regarded as potentially allergic and they remain free from allergic symptoms—with particular reference to asthma—so long as their threshold of tolerance is not crossed.

The allergic balance or tolerance is frequently broken down by recurrent infections and other diseases peculiar to childhood. Among the diseases and conditions responsible for initiating the onset of asthma are the following: pertussis, 15 per cent; acute pneumonia, 14 per cent; measles, 4 per cent; tonsillectomy and adenoidectomy, 3 per cent; and scarlet fever, 2 per cent—a total incidence of 38 per cent.

The most common ailments of man are infections of the upper respiratory tract and when these are superimposed on an allergic rhinitis or bronchitis, they add greatly toward precipitating the onset of asthma. Such infections may also render a person with a predisposition to allergy sensitive to various protein substances. The incidence of upper respiratory infections initiating the onset of asthma cannot definitely be stated for obvious reasons, but it can be safely put at 40 per cent. However, chronic sinusitis as a primary cause of asthma in children is uncommon.

In a large percentage of children the initiation of allergic affections, particularly asthma and hay fever, is brought about by the fact that the children show a positive antecedent family history of allergy, the clinical significance of which is generally recognized. The cause and type of allergic syndrome a patient will develop depends largely upon the environment, nationality, diet, and the section of the country inhabited.

Asthma per se is not inherited but the "soil," "physiochemic make-up," or the tendency to develop asthma, is inherited. One member of a family will have hay fever while another will have asthma or eczema or urticaria. Sometimes the allergic tendency appears to skip a generation, being traceable to grandparents, although the mother and father were free. Pollen asthma and hay fever are more readily inherited than any other clinical form of allergy. Clinical and recent experimental data bring forcibly to light that allergic disease can also be acquired. However, the obtaining of positive family history of allergy cannot be overemphasized and serves as an important clue in the study of the allergic nature of a syndrome under investigation.

PHYSICAL EXAMINATION

A thorough physical examination is essential. A search for structural changes, endocrine dysfunction, gastrointestinal disturbances and for foci of infection, should

be carefully made. The state of nutrition of the child should be noted. Roentgenoscopy of the chest, urinalysis, von Pirquet and intradermal tuberculin tests, are routinely performed. Roentgenograms of the sinuses, blood chemistry, and examination of the blood and nasal secretions for eosinophiles are performed when indicated.

THE TESTS

Time and research have brought out many fundamental facts concerning the tests. We can with some degree of confidence now evaluate all the methods of testing. Every method of testing is employed since experience has demonstrated that one method could not be employed to the exclusion of all others.

We are opposed to the practice of testing every patient with all available allergens, numbering several hundred, for it is an unnecessary waste of time and materials. There are certain allergens that are of sufficient importance to warrant their use in a routine manner. The employment of additional tests can be determined from the history, diet, and environment of the patient.

Selection of Protein.—It is important to select the proper proteins for the cutaneous tests since these substances enable the physician to classify the patient as a positive or negative reactor. It should be emphasized that for convenience of classification the term "negative reactor" is necessary and merely signifies that the patient is refractory to the cutaneous tests though protein sensitiveness may still be present.

The proper selection of proteins by the vast majority of practitioners who are compelled to depend on an outside source of supply has been made more and more difficult. Many pharmaceutical houses market these protein substances. Each concern prepares them differently and some sacrifice potency for convenience of preparation. For the scratch test only dry powdered substances should be used, and for the intradermal test, solutions of known potency which do not irritate the skin.

The Scratch Test.—This is the simplest of the sensitization tests. As a routine procedure and from the viewpoint of safety, the scratch test, especially in children, is the method of choice and is the one with which the study is started. A general or systemic reaction following a scratch test is rare and harmless.

Intradermal Test.—When the scratch test is negative, the intradermal test is employed. We have followed this practice for the last eight years and encountered only a single systemic reaction.

Ophthalmic Test.—Extensive clinical experience has demonstrated that there exists a group of persons whose asthma has definite pollen etiology, who, for some unexplainable reason, exhibit the phenomenon of reacting negatively to pollen with the cutaneous tests (scratch and intradermal technics). These patients are referred to as being refractory to the cutaneous tests. As a means of confirming the diagnosis of pollen allergy in this group of patients, a simple and harmless eye test with natural, pure dry pollen has been employed by us for the last twelve years. This test has demonstrated its extreme practical importance. The majority of the patients with pollen allergy who are refractory to the cutaneous tests suffer from pollen asthma with or without hay fever. A few suffer from vernal conjunctivitis. In other words, patients with uncomplicated hay fever seldom show the phenomenon of negative skin tests with pollen. An occasional patient with pollen asthma who is even refractory to the dry pollen eye test is seen.

Only natural powdered substances are employed for the eye test. For this reason the test seems to be largely restricted to patients with pollen allergy.

Passive Transfer Test.—This method of testing is better known as "local passive transfer." The specific sensitizing substance in the blood has been referred to by the term "reagins." The testing of infants with asthma, and especially those with dermatoses such as eczema and urticaria, at times presents many difficulties. In

these cases the passive transfer technic has been advocated as a feasible method of testing. Unfortunately, the employment of this procedure in a routine manner for the determination of all etiologic factors of allergy is unreliable, and its application as a substitute for the direct methods of skin testing impracticable. However, the local passive transfer test, with its limitation borne in mind, is an important contribution to the science of allergy.

Elimination Diets.—Many workers have reported patients with food allergy in whom protein sensitization was clinically demonstrated with negative cutaneous tests. Rowe emphasized the important rôle that this group played in allergy and introduced a system of "elimination diets" as a means of confirming the diagnosis. These diets are merely "trial and error" diets and include those foods which are known to infrequently cause positive skin reactions or symptoms of allergy in allergic patients. The elimination diets have proved to be helpful and practicable. The biologic grouping of foods as advocated by Vaughan will put the elimination diets on a more rational basis.

GENERAL CONSIDERATIONS

Sensitizations are usually multiple and more frequently encountered in children than in adults. The finding of a cutaneous reaction does not necessarily indicate symptoms. The size or intensity of the cutaneous or ophthalmic reaction to a substance does not determine its importance in the etiology nor does it indicate the degree of constitutional sensitivity present. It has been our repeated experience to observe patients presenting one-plus or plus-minus reactions (scratch technic) who have been improved or entirely relieved of their symptoms when one or all of them were seriously considered as etiologic factors.

It is well known that a majority of the patients have acquired a certain degree of protein tolerance. Some sensitizations have been previous etiologic factors but play no etiologic rôle in the existing cause of the allergic syndrome. Then again sensitization may be present, and symptoms may be due to other factors. With these points in mind it is important, therefore, to differentiate between etiologic and nonetiologic protein sensitization. The nonetiologic sensitization should be regarded as potential factors of allergy.

Etiologic protein sensitization can be demonstrated with ease in some patients. Some require further study and perhaps treatment, before an etiologic sensitization can be found. In another group, the etiologic substances are extremely difficult or almost impossible to determine with any degree of certainty. In this group hospitalizing the patient has proved of considerable help.

It becomes obvious that the clinical significance of the protein skin reactions is far from a closed chapter. It must be borne in mind that the various etiologic protein sensitizations are merely exciting factors and not the basic cause of allergy. What disturbed mechanism is primarily responsible for the varied manifestations of allergy in the human being is still unknown. Until such a mechanism is brought to light, we must content ourselves with the present methods of eliciting the various exciting factors in allergic conditions.

Bronchial asthma is probably the most distressing allergic syndrome the practitioner is called upon to treat. However, before taking up the treatment of asthma with special reference to a practical discussion on the management of the acute attack, we will cover besides other phases of the subject the definition and classification of bronchial asthma of childhood.

DEFINITION, SYMPTOMS, AND SIGNS OF ASTHMA

It has been the custom to define asthma in terms of the acute attack. In other words, the diagnosis of asthma is not generally made unless the patient has been seen in an acute attack of asthma. The onset of asthma may be acute or insidious

with the latter type occurring in the majority of patients. Our definition of asthma, as it affects children, differs from the orthodox conception in that it is simpler and more advantageous to speak of an asthma syndrome and the attack of asthma is merely considered as one of the phases of the syndrome. Asthma is broadly defined as a recurring paroxysmal dyspnea, more marked in expiration associated with wheezing. The revised definition readily lends itself to the recognition of the earlier stages of the disease. Asthma can be divided into three distinct stages: (1) Respiratory oppression is a subjective symptom complained of only by older children and consists of a sense of tightness in the chest and difficulty in drawing a deep breath. No wheezing is present during this stage. Children frequently describe the symptom by saying, "The air stops about here," pointing to the middle of the chest. These children are not infrequently designated as being "neurotic." (2) In the "wheezing or preattack stage" the attack of asthma is absent, and the symptoms are mainly referable to the various asthmatic râles heard in the chest upon auscultation. The dyspnea may be so mild as to escape attention. During this stage the onset of asthma is insidious and is characterized by the appearance of wheezing and dyspnea after repeated attacks of "bronchitis," "rhinitis" or the so-called "noninfectious" cold. They may or may not have direct relation to the season of the year. The symptoms in this stage of asthma are frequently wrongly diagnosed as acute or subacute bronchitis. The spells are often preceded by an upper respiratory infection accompanied by fever. A certain number of children do not progress beyond the second stage of asthma. As a matter of fact, as a result of increased knowledge of allergy on the part of the practitioner, this stage of asthma is becoming more and more readily recognized as asthma and not confused with bronchitis. In children, sibilant and sonorous râles heard throughout both lungs are pathognomonic signs of asthma. (3) The "attack stage" represents the peak of the asthma syndrome. The dypsnea is noticeable and troublesome during this stage of asthma. The intensity of respiratory distress occurs in varying degrees. During the interval between attacks the patient may be completely free from all asthmatic signs and symptoms, or asthma may be continuous from the onset, with varying degrees of remission. The signs and symptoms during this third stage of asthma are too well known to require detailed description.

Status Asthmaticus.—When an attack of asthma has persisted for more than thirty-six to forty-eight hours in spite of repeated injections of epinephrine hydrochloride, then such an aggravated third stage of asthma is referred to as "status asthmaticus." This severe and persistent asthma, if permitted to go on unchecked, will sometimes result in the death of the patient. In other words, the possibility of the occurrence of death in children with status asthmaticus must always be given serious consideration. The old impression that one rarely dies from asthma but from the complications of asthma must be revised.

In connection with severe states of asthma, the question arises as to how long or how severe must a child have asthma before "emphysema" and deformity of the chest occurs. Recurrent attacks of asthma are invariably accompanied by some form of bronchitis and cause an hyperirritability of the bronchial mucous membrane, which may be chronically infected (chronic bronchitis). In a recent series of children with asthma we found that 34 per cent had varying degrees of chronic bronchitis and emphysema (volumen pulmonum auctum). In about one-third of these children a deformity of the chest ranging from mild to severe was also present. It was found that the duration of asthma was the essential factor in chronic bronchitis but not in the production of the "emphysema" and deformity of the chest. It appeared that the more important factors were the frequency, intensity, and the prolonged duration of the attacks. This type of emphysema and deformity differs somewhat from that occurring in adult patients with asthma in whom ossification

of the bones is completed. If the asthma in these children is relieved, one can expect the lungs to be restored to normal and also a considerable reduction in the deformity of the chest.

A severe attack of asthma occurring in a child with a high fever can often be mistaken for an acute pneumonia. It is reasonable to assume that some of these children have small localized areas of atelectasis due to blocking of the bronchioles. A roentgenographic study of over 500 children including over 1,000 roentgenograms failed to reveal a single case of atelectasis, partial or complete, as a complication of asthma. However, a shadow has been observed to occur in one or both bases of the lungs roentgenographically simulating unresolved pneumonia in about 10 per cent of the cases, but differing from it clinically in that a previous history of pneumonia or other infection was lacking and this shadow spontaneously disappeared within two months without any particular treatment. All these patients were nontuberculous. This condition, termed "subacute pulmonary infiltration," at least for the present, should be differentiated from that caused by unresolved pneumonia or delayed resolution. Whether the shadow is a localized allergy in the nature of some form of edema is merely a speculative suggestion.

A child with chronic asthma of long duration, especially of the severe type, is a chronic invalid and of necessity is obliged to live in an adult environment. In other words, they literally live an adult life and are appropriately referred to as being "little old women" or "little old men." These children are usually alert and mentally bright, and, on account of their adult contacts, lead an unhealthy mental existence. These children are usually irritable, "nervous" and "spoiled." They are prone to fretting and sulking and on occasion even work themselves into a state of extreme nervous excitation when denied the freedom of carrying to fruition their every whim. They have learned, like some adults, to bring on attacks of asthma by merely engaging in a tantrum best suited for the occasion. The cause for such attacks must be considered as being a nonspecific secondary factor of asthma. Nevertheless, the problem at times assumes vast importance to the extent of making it necessary not only to separate the child from the parents but also to remove him from his environment.

ETIOLOGIC CLASSIFICATION OF ASTHMA

The protein skin tests, supported by history, physical, and laboratory findings, has made possible a practical method of classification of asthma along etiologic lines. This classification is of extreme value since it leads directly to rational therapy. In this classification there are three main groups which are inclusive of all types of asthma.

A. The protein sensitive asthma group, which comprises about 80 per cent of the cases, includes the positive as well as the negative skin reactors. The diagnosis of protein sensitivity in patients refractory to the skin tests has already been discussed.

B. The nonprotein sensitive asthma group, which comprises about 18 per cent of the cases, obviously includes the negative reactors in whom definite causal allergens could not be demonstrated. The patient in this group gives a history of onset of asthma following infections contracted in the autumn and winter. All of these patients have varying degrees of chronic bronchitis and the relationship between attacks of asthma and infections is quite pronounced. These patients are often referred to as suffering with "bacterial allergy," the proof of which rests entirely on clinical grounds notwithstanding the contention of some workers that a skin test to "bacterial protein antigen" is demonstrable.

C. The paraasthma group comprises about 2 per cent of the cases. Children with paraasthma have thus far proved to be nonprotein sensitive but clinically cannot be distinguished from other types of asthma. From the point of view of etiology and

the existence of certain pathologic conditions which have a direct bearing on the etiology, children with paraasthma must be differentiated from all other groups. These cases are caused directly by an enlarged thymus, by enlarged bronchial lymph nodes (tuberculous or nontuberculous), and also by any other pathologic condition inducing partial tracheobronchial stenosis. This condition is sometimes referred to as obstructive asthma. This is an inadequate term since the majority of the subjects with these abnormalities do not show asthmatic symptoms. In other words, a patient with paraasthma clinically manifests signs and symptoms of asthma plus those of partial tracheobronchial stenosis.

The patients acquiring paraasthma symptoms are inherently asthmatic in type. The symptoms of asthma during the stage of paraasthma are continual as long as bronchial stenosis remains. After appropriate treatment these patients are relieved from all symptoms for periods ranging from two to four years. At the end of these periods symptoms recur, and the condition is diagnosed as bronchial asthma of the nonprotein sensitive type because the factors responsible for the paraasthma are now absent.

The age of onset of asthmatic symptoms in paraasthma is significant. It usually occurs within the first two years of life.

The characteristic symptoms of paraasthma are the gradual onset of asthmatic symptoms with only brief periods of remission from symptoms. The chest reveals the usual signs of asthma, and the roentgenograms in the majority of the cases confirm the presence of the pathologic condition causing the partial stenosis.

TREATMENT OF ASTHMA

The information obtained by the accepted method of allergic investigation has made it possible to place the treatment of asthma upon a rational basis. Any treatment which is based upon causative or exciting factors of disease is indeed worthy of serious consideration.

The treatment of asthma may be discussed under two headings:

1. The treatment of the asthmatic sufferer by specific or nonspecific measures, or both, and by other measures.
2. The treatment of the acute attack.

THE TREATMENT OF THE ASTHMATIC SUFFERER

The ideal treatment of asthma from a specific point of view is the removal of the patient from the offending substance or the removal of the offending substance from the patient. From a practical standpoint it is possible of accomplishment in only a minority of the cases.

Sensitivity to foods is best treated by complete restriction of the offending foods from the diet for a period of at least one to two years. At the end of this time the ingestion of gradually increasing doses is recommended when the allergen is a common food.

The subcutaneous injection of specific allergens is the one method which finds an important sphere of usefulness in cases of epidermal and pollen hypersensitivity. Injections are administered of the more important inhalants when avoidance or complete removal of the offending substance cannot be accomplished.

In allergic children the ingestion or injection of nonspecific substances, while helpful, only accomplish temporary relief of symptoms. As an adjuvant to specific therapy in certain cases, nonspecific measures are at times indicated. Ofttimes

nonspecific treatment is resorted to when the physician is obliged to do something for the patient in whom the etiologic factor of asthma is obscure.

The removal of tonsils and adenoids does not relieve asthma except in a few instances, and then relief is only temporary. The accepted indications for the removal of tonsils and adenoids in nonasthmatic children also apply to asthmatic children. The presence of "sinus disease" invariably denotes a complication of allergy. When treatment is necessary, a conservative attitude is advisable while nasal surgery should be avoided.

In a certain group of cases of asthma the indication for change of environment or climate is clearly defined. Despite this fact, the parents of these suffering children are too often obliged to take matters into their own hands. Under these circumstances such a child is not expected to respond to the beneficial effects of change of environment or climate as satisfactorily as one who is under controlled medical supervision and treatment. Unfortunately, for the refractory chronic asthma sufferer, many allergists decry and even deny the need for change of environment or climate despite the positive evidences to the contrary. Then again, there are far too many practitioners who, to their subsequent embarrassment, unhesitatingly condemn to exile any and all types of asthmatic patients literally to the four corners of the earth without even submitting their patients to the modern accepted standards of investigation and treatment. It is quite evident that rational handling of chronic refractory asthmatic patients will only be accomplished through the medium of education.

THE TREATMENT OF THE ACUTE ATTACK

The management of the acute attack of asthma should be of immediate concern to all practitioners because the acute attack calls for appropriate emergency treatment. Because of the importance of this phase of the subject, it will be taken up in some detail with the hope that the following therapeutic suggestions will afford one an easier and more practicable approach in the handling of children with acute asthma.

The treatment of the acute attack of asthma may be discussed under two headings:

1. The treatment of the acute attack with drugs.
2. The treatment of the asthmatic sufferer with reference to specific allergic factors.

TREATMENT WITH DRUGS

The child suffering with an acute attack of asthma is usually seen at home. Our immediate concern is to relieve the acute suffering. The injection of epinephrine hydrochloride solution (1-1,000) hypodermically is the most effective drug. Depending upon the severity of the attack, 0.12 c.c. to 0.30 c.c. (2 to 5 minims) of the solution is given and in a majority of instances should bring relief in a few minutes, and the earlier the injection is given the smaller the dose is required. In the presence of a severe attack or of an upper respiratory infection, the usual marked relief from epinephrine is often lacking, thus requiring at the end of twenty to thirty minutes a second injection of 2 to 5 minims. Epinephrine can be repeated either in single or in coupled doses as often as is necessary.

Epinephrine is perhaps one of the most useful and at the same time one of the most abused drugs. The dose usually administered to children is entirely too large. Small doses of epinephrine range between 2 and 5 minims. Large doses commence with 7 minims. The effect from 5 minims of epinephrine followed by an injection of another 5 minims twenty or thirty minutes later cannot be compared pharmacologically to a single dose of 10 minims. Furthermore, in a child with chronic asthma requiring frequent injections of the drug, tolerance to epinephrine rarely occurs when small doses are employed no matter how often repeated.

The plea for the use of small doses of epinephrine will be better understood from a perusual of Table I showing in detail the pharmacologic action of epinephrine immediately following the use of small and large doses.

TABLE I

	SMALL DOSES 1 TO 5 MINIMS	LARGE DOSES 7 TO 16 MINIMS
Pulse rate	decreased	increased
Blood pressure	decreased	increased
Cardiac palpitation	usually absent	frequently present
Rate of respiration	decreased	increased
Depth of respiration	increased	decreased
Pallor	usually absent	frequently present
Tremor	usually absent	frequently present
Other vasomotor symptoms	usually absent	frequently present

It is of clinical interest to note that in adults with systolic blood pressures ranging as high as 240 mm. of mercury the injection of 2 minims of epinephrine will do no harm and in a majority of instances cause a temporary fall of systolic blood pressure ranging from 20 to 40 mm. with relief of asthmatic symptoms.

It is true that in most children a large dose of epinephrine will relieve an attack of asthma sooner than a small dose, but it is also true the unstable nervous system common to childhood becomes more unsteady resulting in a chain of symptoms which often alarm the patient and parents.

In "status asthmaticus" where asthma has continued uninterruptedly for more than thirty-six to forty-eight hours in spite of subcutaneous injections of epinephrine, a slow intravenous injection of from 0.06 c.c. to 0.12 c.c. (1 to 2 minims) of epinephrine (1-1,000) diluted with the patient's own blood or with sterile physiologic salt solution, and repeated as often as is required, has proved to be a life-saving measure. Hospitalization, preferably to a public ward, must be resorted to when intravenous epinephrine injections fail to relieve the patient from his state of "strangulation." Not infrequently, such a child becomes remarkably improved from twenty-four to thirty-six hours after hospitalization.

The use of oxygen in ordinary attacks of asthma is not necessary, but in severe asthmatic states and in status asthmaticus it may be employed with some benefit to the patient. Oxygen at room temperature in a concentration of 50 per cent only should be used. The administration of oxygen through the simple nasal catheter is practical and useful.

Ephedrine sulphate, preferably hydrochloride, is employed orally in doses of 0.03 gm. (½ grain) and is of use only in mild cases. It does not usually prevent attacks of asthma and for this reason should not be empirically employed. The indications for ephedrine should be the same as those for epinephrine. The prolonged administration of ephedrine usually results in a tolerance for the drug. Some of the unpleasant symptoms induced by ephedrine are weakness, restlessness, nausea, vomiting, insomnia, malaise, tremors, palpitations, chilly sensations, and bladder disturbances. To overcome some of these objectionable symptoms a synthetic ephedrine-like drug, such as ephetonin 0.03 to 0.045 gm. (½ to ¾ grain) or 0.02 gm. (⅓ grain) of neosynephrine hydrochloride may be employed with some benefit, although the latter drug is somewhat less active than ephedrine ephetonin. It should be borne in mind that ephedrine cannot replace epinephrine and that when the former drug fails to relieve asthma then an injection of epinephrine must be administered. Ephedrine is a useful drug when its limitations are understood.

The use of emetics is no longer fashionable.

The use of atropine is of little value. Atropine often prolongs the attack by drying up the secretions and should never be given when the patient has an intercurrent respiratory infection.

The hypodermic administration of morphine must be used with extreme caution. In cases of "status asthmaticus" the drug is practically contraindicated. In this latter state with the patient in a continuous struggle for air, as evidenced by the rapid rate of respiration and cyanosis, the injection of morphine, which lowers the respiration, may literally "drown the patient in his own secretions." Deaths following the use of morphine are not infrequent. For the ordinary attack of asthma morphine can be used with safety but is certainly not indicated. However, when one wishes to employ in a selected case a small dose of morphine, just sufficient to control temporarily the nervousness but not enough to affect the rate or depth of respiration, dilaudid 1/40 to 1/60 grain can be employed with safety. Dilaudid does not cause vomiting as readily as morphine, especially when given in conjunction with epinephrine.

Inhalation of the fumes from burning the popular powder "cures" frequently gives temporary relief if the attack is mild. The powder generally contains potassium nitrate and the dried leaves of stramonium. The fumes have an extremely irritating effect on the bronchial mucous membrane and for this reason should not be employed.

Inhalation of "dry" vapors generated from an electrical nebulizing apparatus containing some epinephrine preparation during mild attacks of asthma frequently dispenses with the injection of this drug. It does not cure asthma.

Drugs employed for the relief of cough depend upon the type of cough and the stage of bronchitis treated. In the early stages of bronchitis a stimulating expectorant, as ammonium chloride, 0.12 to 0.3 gm. (grains 2 to 5) in conjunction with codeine sulphate 0.006 to 0.01 gm. (grains 1/10 to 1/6), should be given every three to four hours for about one week. If the cough is "soft" or persists with some expectoration of sputum, ammonium chloride is replaced with sodium iodide, 0.12 to 0.3 gm. (grain 2 to 5), and given three times daily. Children from ten to fourteen years of age with much expectoration of sputum are frequently relieved when codeine sulphate is combined with terpin hydrate 0.2 gm. (grains 3) and taken every four hours. In the presence of a nonproductive spasmodic cough, the following combination helps considerably: antipyrin 0.06 to 0.12 gm. (grains 1 to 2), codeine sulphate 0.006 to 0.01 gm. (grains 1/10 to 1/6), and sodium bromide 0.4 to 0.8 gm. (grains 6 to 12), to be taken every four hours. Calcium is of no value.

TREATMENT WITH REFERENCE TO SPECIFIC ALLERGIC FACTORS

Children who have had the benefit of allergy study need only have their diet and environmental contacts rechecked in order to make certain that new factors in the etiology of asthma have not arisen.

For the cases which have not been allergically studied and until such a time presents itself when the patient can undergo a complete allergic investigation, the following procedure can be employed:

A detailed history of the case should be obtained.

The child should be kept in bed until the attack of asthma has completely subsided.

With the onset of the attack the child usually refuses all food. Hot sweetened liquids should be pushed to prevent an easily induced acetonemia. If vomiting is present, a glucose saline retention enema will help. In the absence of vomiting the first foods that can be given with comparative safety are apple sauce, baked apple, stewed prunes without the skin, stewed or canned peaches and pears. In older children small quantities of hot skimmed milk can usually be tolerated. Citrous fruits

in any form rarely cause asthma. In another day or two, well-cooked vegetables such as string beans, spinach, carrots, beets, asparagus, or potato are given. Pure rye in the form of ry-krisp with orange jello, rice, tapioca, cornmeal, and later a lamb chop may be given and are usually well tolerated, as well as olive oil, lettuce, salt, maple syrup, gelatin, and canned pineapple. All of the foregoing foods are gradually added to the diet. A new food, if tolerated, can be added to the diet every third or fourth day. Symptoms of intolerance to a food sometimes do not become manifest for from twelve to thirty-six hours after ingestion. Cold drinks and ice cream are forbidden. Wheat, eggs, and fish are added to the diet last or until after the patient has undergone allergic study.

Investigation into the environmental contacts first takes into consideration the patient's bedroom. Every effort should be made to free the room of as much dust as possible. All floor coverings and window draperies are removed. All the closets are cleared of as much clothing and storage as possible. The floor and walls, bedstead, and springs are to be washed with soap and water. Quilts are good collectors of dust and should be removed. As a matter of fact, direct contact with mattress and pillows more than six months old frequently cause trouble because of the accumulation of dust or other allergens. For this reason it has been found more economical and safer to cover the bedding with a dust-proof material such as Du Pont's fabricoid or a heavy durable rubber. The mattress and pillows are encased in this material. Use only cotton and wool blankets encased in linen sheets and washed with soap and water at least every two months. While the room is being prepared, the child should be removed to another part of the house. Sometimes it becomes necessary in certain cases to clear the remainder of the house of all rugs and draperies besides subjecting the floors and walls to a thorough cleansing. The vacuum cleaner is to be freely applied. All domestic animals are forbidden in the house. Talcum powder is not to be used, nor is the child's attendant permitted to use perfumes or face powder containing orris root. Visitors working in dusty occupations or those who have been exposed to animal emanations should not enter the house, much less the child's room.

The question of temperature and humidity of the room in which the child sleeps is an important one. Should the windows be opened or closed? In the mild months of the year the windows can be opened provided they are screened. The bed should not be located in the direct path of the currents of air coming through the window. In the cool months of the year and especially during the winter, it is preferable to have the bedroom windows shut and fresh air can be allowed to filter in through the open door from open windows in the adjoining room. Fresh cold air, particularly during the early morning hours, causes patients to cough and frequently induces asthmatic attacks. Hot air or steam radiators cause excessive dryness of the air and in conjunction with cold air predispose the patient not only to asthmatic attacks but also to upper respiratory infections. To prevent the humidity of the child's room from dropping below 50 per cent the top of the radiator is covered with a wet turkish towel. A child living in a room with a normal humidity and a temperature ranging between 68° and 70° F. along with all of the foregoing allergenic environmental and dietetic corrections can be considered from the standpoint of allergy as receiving appropriate emergency treatment.

If a patient is seen during a pollen season and the history indicates a pollen asthma and if the asthma is severe, it is not advisable to institute immediately coseasonal pollen hyposensitization treatment. Such a patient is most likely suffering with a pollen toxemia, and the injection of pollen extract, no matter how small the initial dose, may only aggravate the asthma. Under these circumstances the child should be sent to and kept in an atmosphere free from the offending pollen. This can be accomplished by sending the patient, if economic conditions permit, to a locality known to be relatively free from the offending pollen. Otherwise the

child can be placed in a room made free from dust and pollen by reliable air filters. In such an environment the patient often requires as long as one week before the asthma is cleared, after which coseasonal pollen treatment can be commenced. Some untreated patients continue to suffer with asthma even after the pollen season has terminated. This state is referred to as a pollen "hangover" and should be recognized as such because these patients respond very favorably to specific pollen hyposensitization treatment. The treatment should be instituted as soon as the diagnosis is confirmed by appropriate allergic study.

DISCUSSION

DR. H. H. DONNELLY (WASHINGTON, D. C.).—Dr. Schick, would you elaborate some of the points you made, for example, on the vaccinia test. How can you tell when a patient is immune to vaccinia?

DR. SCHICK.—The easiest way is to employ the old method of scarification rather than the newer intracutaneous technic of vaccination. There is a distinct difference between first vaccination and revaccination. With the latter one can tell after a few days whether the individual is still immune. The stages of development of a vaccinia reaction are very characteristic. Unfortunately, too many physicians look for the pustule for the first time some two weeks after the scarification. They are not entirely familiar with the development of the reaction. In the first two days after vaccination nothing is visible. On the third day a tiny infiltration appears. This grows, as Pirquet stated, like a bacterial culture on an agar plate. One can assume that the vaccine virus grows on the human skin as a culture media. First, there is a slight local redness which spreads, and then in the center there develops a little vesicle. Later, this vesicle becomes darker and pushes the red ring in front of it. From the ninth to the eleventh day there appears a large redness, erysipeloid in character, and at this moment further growth of the central vesicle is inhibited. This is the result of the appearance of antibodies. From now on regressive symptoms develop and are manifested by a drying up of the center lesion alone with a desquamation of the erysipeloid wheal. If a child immune to vaccinia is revaccinated, there may appear for a few hours after vaccination some redness or perhaps after two or three days only a little vesicle. The symptoms appear earlier, and the whole vaccination process is finished earlier. This immediate or accelerated reaction indicates the presence of immunity.

Years ago when teaching the history of vaccination to my students I related an interesting story of a physician who, several years after the discovery of vaccination, tested the potency of vaccine virus by making a scratch test with the vaccine on his hand. In order to perform vaccination at that time it was the custom for this physician to visit three or four villages during a day, and prior to starting on his rounds the scratch test was made. A sign of the potency of his vaccine was the appearance of a little redness and an itching sensation at the site of the test. I believe the itching sensation felt in a vaccination and revaccination is very characteristic. Revaccination of an immune individual does not lead to scar formation. If symptoms appear similar to a first vaccination, one can safely infer the patient was not immune. If the child gets an accelerated reaction but otherwise similar to a first reaction, it shows that the immunity is declining. Full immunity would show a slight or minimal reaction. Does that answer the question?

DR. DONNELLY.—In part; it is a very nice way of explaining it, but it does not answer it entirely. You have not made clear to my mind the distinction between complete immunity and allergy. Now, for example, if a child is vaccinated with the full course of a primary vaccination and two years later he is revaccinated and then develops or goes through essentially the same course as in the primary

vaccination, perhaps a little earlier and a little shorter course, is the child at the time of revaccination immune, partially immune, or not immune at all?

DR. SCHICK.—The child is not immune because his reactivity shows he did not get any benefit from the first vaccination. You can say the child shows only a slight difference in reaction. I would state that such a child in time of exposure is in danger of contracting real smallpox. A small difference in the time of development of the reaction occurs also at the first vaccination. It is known, for instance, if ten vaccination scratches instead of three are made that from the increased stimulation and the formation of more antibodies the incubation period will be shortened. These small differences in the incubation time are not sufficient evidence to base a diagnosis of the presence of immunity.

It is difficult to correlate the terms "antitoxic immunity" on the one hand and "allergy and hyperergy" on the other. For this reason Pirquet chose a new term. On the one side you have antitoxic immunity which leads to complete absence of reaction; on the other side, allergy and hyperergy lead to a quick reaction, but one should realize that the reaction is frequently so minor that the patient is practically immune even if he is hyperergic, e.g., he does not show any clinical symptoms. A diphtheria patient given antitoxin becomes immune and develops no reaction. An allergic person not only gets a reaction but a very quick one, so quick that the virus is killed off almost immediately. If you inject such an individual with large doses, he will be worse off than the person who has never been injected. For instance, a tuberculous infected individual is worse off if superinfected with a large dose. Going back in the history of smallpox, you will find that the most virulent and fatal form of hemorrhagic smallpox occurs occasionally in vaccinated persons. Why this occurs in vaccinated persons and why so virulent a condition is difficult to answer. A violent reinfection in a very hyperergic individual may lead to a similar ending. The more time that has elapsed between vaccination and reexposure the greater the loss of humoral antibodies. Finally, all humoral antibodies disappear, but there is still the capacity to form antibodies more quickly than the first time.

DR. DONNELLY.—Is complete vaccinal immunity a temporary state? Does it disappear very quickly and does not allergy develop?

DR. SCHICK.—For the first two years after vaccination the immunity may be very good, but after that it gradually disappears. At the end of the second year you will get almost no reaction. Frequently, after seven to twelve years, full reactivity is reestablished. And for this reason revaccination is advisable some time after the seventh year.

DR. DONNELLY.—Why are the newborn so resistant to vaccination?

DR. SCHICK.—This is not absolutely correct. Early in the history of vaccination it was discovered that the newborn may have a very mild form of vaccinin without elevation of temperature. We know the skin is very slow in producing antibodies and that the newborn child is rather anergic against different toxins. We may have a negative diphtheria toxin reaction in the newborn in spite of the absence of antibodies. The nervous system of the newborn is not fully developed. I have once employed the expression that the skin of the newborn child is still asleep. The irritability of the nerves appears necessary for the development of reaction. Spies has shown that the application of anesthetics on a wound hastens healing. Another theory accounting for the milder reactions encountered in the newborn is the transmission of immunity from the mother.

DR. FRED W. LATHROP (PLAINFIELD, N. Y.).—Concerning the relationship between allergy and immunity, when one uses "cold" vaccine or typhoid vaccine

in growing infants is one reducing hyperergy or building up allergy? Should small doses of vaccine be employed to produce a local reaction, or do you want a violent reaction?

DR. SCHICK.—I believe a state of hyposensitization is what is needed. The child already has antibodies, otherwise it would not be so sensitive (hyperergic). I have gone through all the phases of tuberculin treatment with small, intermediate, and large doses. Some workers thought it best to maintain the hyperergic reaction and so injected only that quantity of tuberculin which caused a continuation of activity. If the activity was too low, then the amount of tuberculin injected was increased. The other speculation was that the patients became hyperergic. I do not think they became immune. I favor the use of small doses, the avoidance of local reactions and the gradually increasing doses.

DR. F. P. GENGENBACH (DENVER, COLO.).—Dr. Peshkin spoke about the use of sodium iodide in clearing up the asthmatic cough. Does he think it does any good to use iodides continuously between the attacks? There is nothing else that seems to lessen the recurrence of the attack.

DR. PESHKIN.—The continuous use of iodides over a period of many months with intermissions of from one to two weeks in patients with a complicating chronic bronchitis seems to be efficacious in lessening the severity and frequency of the attacks of asthma.

DR. GENGENBACH.—It is my experience that children tolerate syrup of hydriodic acid better than sodium iodide.

DR. PESHKIN.—It really does not matter what form of iodides is used, so long as the patient gets the drug.

DR. GENGENBACH.—We have vaccinated several hundred newborn infants against smallpox and had "takes" in every case; in other words, these infants were not immune to smallpox. They had no fever as a result of the vaccination, and the reactions were very small but definite.

DR. SCHICK.—It will be of interest to recall that in the Foundling Home in Vienna in 1801, five years after the publication of Jenner's work, all newborn children were vaccinated. It was observed then that the reactions were very mild and frequently without an elevation of temperature.

DR. DONNELLY.—They used humanized virus. What virus did Dr. Gengenbach use?

DR. GENGENBACH.—Lederle's smallpox vaccine.

DR. DONNELLY.—The vaccine we employ now is dilute calf lymph. The lymph must be potent in order to get 100 per cent "takes" in the newborn.

DR. GENGENBACH.—One shipment of virus used on twenty-five infants we think was not properly kept either before or after receiving it. In these infants there were no "takes"; but on subsequent revaccination with another virus, there were 100 per cent "takes." We felt there was something wrong with the first shipment of virus; otherwise we would have had no "takes" in the twenty-five infants revaccinated.

DR. DONNELLY.—I would like to ask Dr. Peshkin what his proof is that vernal catarrh is an allergic manifestation.

DR. PESHKIN.—I am glad Dr. Donnelly brought this question up for discussion since most allergists and nearly all ophthalmologists deny that vernal catarrh

is an allergic condition. Before it is possible for you to become sympathetic to my contention that vernal catarrh is allergic in nature, it becomes necessary to give a brief history of the evolution of the recognition that persons can actually suffer with pollen allergy (asthma with or without hay fever) and yet react negatively to pollens with the cutaneous tests (scratch and intradermal technics). We recognized this fact in 1922 and collected our first series of cases. As a means of confirming the diagnosis of pollen allergy in this group of patients, a simple and harmless dry pollen eye test was employed, the technic and interpretation of which was later perfected and published in the *Journal of Allergy*, November, 1931. Later it was recognized that there also exists a small group of patients who suffer with classical symptoms of pollen allergy and yet fail even to show a positive dry pollen eye test. These patients are referred to as being refractory to pollen with the cutaneous and ophthalmic technics. The treatment of these refractory pollen cases consisted of inoculation with specific pollen extracts. The extracts employed contained the pollens known to cause allergy during the months the patient's symptoms were prevalent. The results of treatment were uniformly good, and these results in the large majority of the cases were obtained only because large doses of concentrated specific pollen extracts were employed. When a group of these patients were injected only with nonspecific antigens or autogenous vaccines, the results were nil.

My interest in vernal catarrh from the viewpoint of allergy was stimulated in 1922 by the late Dr. Cyril Barnert, ophthalmologist to Mt. Sinai Hospital, New York. He referred to me a boy, aged thirteen years, with severe vernal catarrh of four years' duration. The patient was treated by all the leading ophthalmologists of the city without relief. Radium application to the lids was suggested as a last resort. Dr. Barnert at that time felt the risk of deformity of the lids resulting from radium treatment was too great and besides was inclined toward the supposition that the basis of vernal catarrh was pollen allergy. The child showed by scratch test positive reactions to all the pollens of the gramineous group—timothy, red top, orchard grass, June grass, etc.—but negative reactions to the short and giant ragweeds. The patient was subjected to a thorough preseasonal course of pollen hyposensitization treatment; the extracts of mixed grasses and mixed ragweed were injected. It was our fortunate experience to have afforded this patient almost complete relief of all symptoms of vernal catarrh except for slight discomfort in April and the early part of May. The large majority of the subsequent cases of vernal catarrh coming under my observation were negative to all pollen with the cutaneous tests, and some were even negative to the dry pollen eye tests. Specific treatment with pollen extracts, however, gave uniformly good results in most of these cases. In the light of these experiences it was, therefore, fairly safe to conclude that most patients with vernal catarrh, so far as their refractoriness to pollen cutaneous tests and their favorable response to specific pollen treatment were concerned, were comparable to a similarly treated group of patients with pollen asthma and hay fever.

From an allergic standpoint vernal catarrh can be regarded as a localization of sensitization of the mucous membranes of the lids to pollen antigens. It is known that there exists a certain group of patients with pollen allergy in whom the symptoms of allergy are entirely confined to the bronchial tubes and are manifested by spasmodic bronchitis or usually bronchial asthma. Therefore, we have felt on the basis of these facts that our attitude on the treatment of vernal catarrh with pollen extracts was reasonable and warranted. The secret in the successful treatment of vernal catarrh is not the danger of employing the wrong pollen mixture but rather the tendency to employ insufficient treatment, i.e., underdosage. We have found that these patients require large doses for maximum protection.

It might be of interest to know that some of my patients with vernal catarrh subsequently evidenced other manifestations of pollen allergy, such as hay fever and pollen asthma. This is further positive evidence of the pollen etiology of vernal catarrh.

It will be noted that in the treatment of our cases of vernal catarrh only extracts of mixed grasses and ragweeds were used, in spite of the fact that symptoms of this condition start as early in some cases as March. We have come to recognize that the early symptoms of vernal catarrh are in reality due to the trees, but, since the eye symptoms in most patients were not troublesome nor continuous during March and April, we felt that the addition of tree pollen extract to the treatment was not necessary. It is of interest, however, to relate a case of vernal catarrh occurring in an adult (whose son has ragweed hay fever), whose symptoms of vernal catarrh commence at the end of April and terminate the end of July. Treatment with extracts of oak and mixed grass pollen has brought almost complete relief for the past two years.

It can be conservatively stated that our results of treatment of vernal catarrh with specific pollen extracts in 1934 are comparable to those of 1922. In other words, after twelve years we are still getting good results, and, until a more logical, basic, efficacious form of treatment is discovered, we feel justified for the present in maintaining our optimistic attitude toward the treatment of this phase of pollen allergy.

DR. DONNELLY.—What did passive transfer tests show?

DR. PESHKIN.—This question embodies the inference that a negative passive transfer test is evidence that allergic sensitivity does not exist. It is our recollection that Dr. Coca and his coworkers held or still hold the belief that a positive skin reaction obtained by direct testing and not showing up on passive transfer can be regarded as a pseudo- or as a nonallergic (nonatopic) reaction. These views are untenable when one weighs the mass of evidence to the contrary. It is a known fact that when allergic individuals react negatively to cutaneous tests the passive transfer tests are also expected to react negatively. This was demonstrated by Dr. A. H. Fineman and myself in 1929 on a small group of patients with definite pollen allergy who exhibited the phenomenon of reacting negatively to pollen with the cutaneous tests (scratch and intradermal technics). Likewise, patients with vernal catarrh with negative pollen cutaneous reactions will not show positive passive transfer tests. It will be of interest to report at this time that we have been successful in abolishing the cutaneous reaction (scratch and intradermal technics) to pollen in a small series of patients after repeated courses of pollen treatment. With the skin in this state of refractoriness to pollen, the passive transfer tests were also negative. However, the clinical results from treatment in these cases did not parallel the negative skin and passive transfer tests. It is quite evident then that the presence of a positive skin or passive transfer test merely indicates positive evidence of allergy and that an absence of these reactions in persons with a positive history of intolerance to pollen or other substances does not rule out allergy.

DR. DONNELLY.—I am unconvinced with regard to vernal catarrh. I am sure that there may exist a food sensitivity without positive skin and passive transfer tests, but with the inhalation of pollen I am not convinced.

DR. PESHKIN.—What fundamental differences can there exist between cutaneous pollen refractoriness and food refractoriness? I do not know of any other evidence than that which I have already presented to convince you that vernal catarrh is allergic in origin except to invite you to examine personally these patients under my care. I wish to state that all persons with vernal catarrh under my care have been diagnosed and treated by competent ophthalmologists to no avail.

DR. S. J. LEVIN.—I would like to hear something about tonsillectomy in asthma.

DR. PESHKIN.—For many years the impression has prevailed that enlarged tonsils and hypertrophied adenoids played an important part in the causation of asthma. As early as 1912, Still of London found, however, that such an assumption was wholly unwarranted. In more recent years and especially since the introduction of the protein skin tests, evidence has accumulated pointing to the fallacy of associating tonsils and adenoids with asthma. We investigated this question and incorporated the findings in a paper published in 1927.

In was found that the operation for tonsillectomy initiated the onset of asthma in 3 per cent of the cases. The removal of tonsils and adenoids did not relieve asthma except in one instance, and in that the relief was only temporary. These observations would indicate that enlarged or diseased tonsils and adenoids do not operate as etiologic factors in asthma. On the other hand, surgical intervention may initiate the onset and adversely affect the course of asthma temporarily. The indications for the removal of tonsils and adenoids in children with asthma are the same as for children without asthma.

DR. LEVIN.—Do you think that tonsillectomy performed during the pollen season predisposes to hay fever?

DR. PESHKIN.—Obviously, yes. In inherently allergically predisposed persons, mucous membranes traumatized during the pollen season facilitate the absorption of foreign protein by an increased permeability of the tissues. This question is best answered by the case of a child who sleeps on a feather pillow and is sensitive to feather epithelium and yet gets an asthmatic attack only with an intercurrent upper respiratory infection. The mother frequently insists that the feather pillow is not the cause of the asthma but rather the susceptibility of the child to upper respiratory infection, because during the intervals of freedom from infection the child remains free from asthma in spite of continuous exposure to feathers. This is explained by the fact that the child has considerable tolerance for the sensitizing protein under normal conditions. It is common knowledge that such factors as intercurrent diseases or infections have a marked influence on tolerance. The development of respiratory infection, however, with its incidental congestion and inflammation of the mucous membranes, possibly makes the membrane more permeable to the sensitizing substance. The occurrence of the infection in the absence of exposure to feather epithelium usually leaves this child free from asthma.

DR. LEVIN.—Is there any relationship between delayed reaction following intradermal test and delayed clinical symptoms?

DR. PESHKIN.—Most workers feel the existence of such a relationship has not been borne out by the clinical facts.

DR. JOSEPH LINDE (NEW HAVEN, CONN.).—In the case of an hyperergic youngster, eight years old, with eczema and in whom the eczema was aggravated on several occasions by acute tonsillitis, the dermatologist has suggested the use of an autogenous vaccine made from the throat as a therapeutic measure. What do you think?

DR. PESHKIN.—I do not believe there exists a primary causal relationship between the eczema and the attacks of acute tonsillitis in your patient. Tonsillitis can play a contributory rôle. If you use an autogenous vaccine and get a clearing of the skin in this particular case, one can state with little hesitancy that the favorable results were brought about because of nonspecific and not specific therapy.

DR. LATHROP.—What about "stool vaccine"?

DR. PESHKIN.—A vaccine cultured from the stool may in most instances be considered as another form of bacterial nonspecific therapy. Sometimes a "stool vaccine" is a more potent form of nonspecific therapy than a "respiratory vaccine," and for this reason the top doses employed with the respiratory vaccine are usually larger than those with the stool vaccine. The top doses, which range from 0.5 to 1 c.c., can be maintained at weekly intervals for months. Since allergic persons vary in their response to different forms of bacterial vaccines, it is no wonder then that a wide variety of substances other than bacterial vaccines have been found useful in the nonspecific treatment of asthma. It should be emphasized that dosage of nonspecific substances employed in children should not evoke a general reaction as manifested by an elevation of temperature or an aggravation of symptoms. The injection of these antigenic substances is essentially stimulation therapy. The dangers of overdosage are overstimulation and consequent exhaustion of the defensive mechanism with resultant aggravation of symptoms. In other words, the desired goal is nonspecific hyposensitization and not hypersensitization.

Next to bacterial vaccines milk is probably the most commonly employed nonspecific agent in the treatment of patients nonsensitive to the protein. Commencing with 0.5 c.c., injections are given three times a week, increasing by 0.5 c.c. until 3 c.c. doses are reached. Smaller doses from 0.5 to 1 c.c. of fat-free milk given in conjunction with stock or autogenous bacterial vaccine twice weekly are frequently helpful. The effectiveness of milk seems to be dependent largely upon its bacterial content, and for this reason milk freed from bacteria is not nearly as effective.

Peptone is a less effective nonspecific substance. A 5 per cent solution (Armour's Peptone No. 2) subcutaneously injected beginning with 0.3 c.c. twice weekly and slowly increasing until the dose of 2 to 3 c.c. is reached. If improvement occurs, then the dose is gradually decreased and the intervals between injections increased to a week. Most peptones are made from beef and should not be employed in beef sensitive persons.

Witte's peptone given by mouth in capsules (0.5 gm.), forty-five minutes before meals as a nonspecific agent in food allergy appears to have some limited value.

Autohemotherapy and autohemoserotherapy is employed with favorable results. Injections of the patient's own blood or serum are used. Whole blood is quite as satisfactory as serum. Blood is drawn directly from a vein at the elbow (10 c.c.) and is immediately reinjected subcutaneously or intramuscularly into the lumbar region or buttock. Injections are repeated at intervals of three or four days and later at greater intervals.

Snake venom (Crotalus atrox or horidus) injected intramuscularly at weekly intervals starting with 0.12 mg. (1/500 grain) is of some value as a nonspecific treatment. The injections are given in gradually increasing doses until a top dose of 0.6 or 1.2 mg. (1/100 or 1/50 grain) is reached, after which injections are administered weekly or twice monthly for many months. The pain incident to the injection of crotalin can be minimized with 0.5 c.c. of a 2 per cent solution of novocaine.

It should be borne in mind that nonspecific therapy at its best is merely a palliative measure and offers a temporary relief from symptoms for varying periods of time. The many types of nonspecific treatments employed for adults, particularly those inducing fever, cannot be safely applied to children, and for this reason only the foregoing therapeutic measures were considered.

With any form of nonspecific therapy a large local reaction is a contraindication to an increased dose. The various nonspecific measures employed in asthmatic children are frequently used as adjuvants to specific therapy.

DR. GENGENBACH.—In a case of asthma with persistent bronchitic symptoms with a sputum culture of nonhemolytic streptococcus, do you think a nonspecific vaccine will do any good?

DR. PESHKIN.—Whenever feasible, autogenous vaccine should be used as a first choice because there always exists the possibility of finding a patient in whom the treatment may be specific in nature. With this exception the use of some form of nonspecific treatment will suffice.

DR. SCHICK.—You referred to the peptones as a nonspecific agent. Dr. Urbach of Vienna has introduced the use of a specific peptone which he called "propeptans." Each protein of food has a specific peptone. For treatment the commercial peptone is insufficient since it is prepared only from beef protein. One-half an hour before the meal the specific propeptan of every foodstuff is given by mouth. Last year Dr. Urbach published a paper on the use of propeptans in pollen allergy. The reports from some workers confirm the good results obtained by Urbach. My own experience is limited. I think the idea is interesting and the work should be carried on.

(The remainder of the discussion followed Dr. Schick's and Dr. Peshkin's talks repeated for the second Round Table, Tuesday, June 12.)

DR. EARL W. MAY (DETROIT, MICH.).—May I ask Dr. Peshkin if he has used benzedrine?

DR. PESHKIN.—Our experience with benzedrine has been limited. The inhaler contains benzyl methyl carbinamine carbonate, which, when exposed to the air, liberates nascent fumes and appears to have an ephedrine-like action on the mucous membranes but of a lesser degree. The local application of a solution of ephedrine sulphate to the nose is being rapidly replaced by a less irritant and equally efficacious drug in neosynephrine hydrochloride employed in a 1 per cent solution.

DR. C. E. BRADLEY, JR. (TULSA, OKLA.).—The field has been broadly covered, but there remain several topics which are exceedingly important to all of us and therefore warrant some discussion. A large number of children are susceptible or have an idiosyncrasy to sodium iodide. This drug should not be given when starches have been freely ingested because an encapsulated iodide compound is formed and the therapeutic effect is lost. The drug I have found of value in over twenty-five years of clinical work in the Southwest is syrup of hydriodic acid. One should be cautioned to have the syrup of hydriodic acid compounded by a reliable pharmacist because this compound deteriorates when old. Lobelia is a most admirable antispasmodic, and in mild asthma 75 per cent of the patients can be relieved with this drug alone provided that it is freshly prepared. Five minims of the tincture of lobelia per 15 pounds of body weight are given every three or four hours. Ammonium chloride is purely a gastric irritant, and I have not been able to note any beneficial clinical effect from its use. It induces nausea with an excess of mucus coming from the stomach and does not relax the spasm. The thing we want to do is to relieve these children and not distress them.

DR. PESHKIN.—The recital of clinical experiences with drugs is always interesting. Different workers have different viewpoints and varied experiences with the same drugs. Dr. Bradley is quite satisfied with his results from the drugs he uses. However, our experience with sodium iodide in some thousands of asthmatic children in the doses recommended has not left us with the impression that this drug is so easily intolerated. As a matter of fact, drug idiosyncrasy (allergy) in asthmatic children is relatively uncommon. It is to be regretted that we cannot confirm the statement of Dr. Bradley with reference to lobelia. This drug has been

in use for many years. If it possesses the favorable action as claimed by Dr. Bradley, the drug no doubt would have been acclaimed by the medical profession long before this. Ammonium chloride appeared to be well tolerated in the large majority of the children to whom it was administered.

DR. C. A. STEWART (MINNEAPOLIS, MINN.).—With all respect to our Chairman, I do not agree with some remarks made in his introduction. In the study of children at Lymanhurst, our tuberculosis institution, allergy is found. We find that some children are extremely sensitive to the extent that very small doses of tuberculin do damage and that sensitivity at the site of the lesion is higher than at the skin. We find that small doses of tuberculin added in the presence of allergy give a severe reaction. I think this has been well demonstrated by Rich and Cortez and by Cross of Minneapolis that allergy and immunity are separate things.

Dr. Schick referred to small doses. He is treading on thin ice for the following reason. Tubercle bacilli once ingested in the human body multiply and continue to multiply until allergy develops. By the time allergy develops the sensitiveness to tuberculin, some time has elapsed, and we do not know how long it takes for the bacilli to spread to other parts of the body where they may live for years. If we could guarantee that our doses were small, that the first dose was small and that the second dose was small, the situation would be fine. At Lymanhurst we have lost only one child, which fact indicates that the normal body is equipped with resources to combat reinfection. I think we work with a handicap when we look upon this allergy, the primary tuberculosis with all the changes and complications that are produced in the body, as the preliminary stage of all the clinical forms of tuberculosis that occur in man. It is on these points, Dr. Schick, that we are not in accord.

DR. SCHICK.—I am very glad Dr. Stewart spoke. It is always good for us when somebody speaks up and takes a different and new attitude on a subject. I am thankful that this whole question has come up in the last few years as a result of the work of Dr. Stewart of Minneapolis and Dr. Rich of Baltimore. I was present in London when Dr. Rich read his paper on the hyperergic reaction. I should like to mention the fact that we should always be a little careful by not going too far. You will recall that in central Europe, especially Vienna, about 95 per cent of the children at fourteen years of age were infected with tuberculosis. You must admit to the correctness of our original contention that the number of persons with tuberculosis almost reaches 100 per cent. These figures, however, cannot be applied to other parts of the world. In New York City tuberculous infection is present in 48 per cent of the children; this takes into consideration a large colored population among the hospital patients. In other communities the percentage ranges down to as low as 14 per cent. Vienna with its 95 per cent of positive tuberculin reactions at the time of puberty would be in a terrible state of affairs if this infection with tuberculosis was so dangerous. I cannot conceive how Vienna otherwise could have existed so long.

I believe the truth of this whole question will eventually be found in the middle of the course. I am entirely open minded. I would be willing to accept the viewpoint advanced by Dr. Stewart after additional proof and more years of experience. Time alone can decide which viewpoint is nearer the truth. I may be entirely in error. I hold that allergy cannot be harmful. Does not vaccination against smallpox produce allergy? Is this allergy not beneficial and would Dr. Stewart abandon vaccination against smallpox?

DR. STEWART.—If 90 per cent of all cases of smallpox appeared in people who had "scars," we would demand the abolishment of vaccination. If you take some 10,000 children and watch them over a period of years and observe bone, joint,

and kidney tuberculosis come in groups that were originally allergic, can you say that allergy was an advantage? We have observed no group of infections that were benefited by the first infection.

I would like to ask Dr. Schick what he thinks. We have never seen a person develop primary tuberculosis a second time who did not react differently the second time. The boy who raised the flag at Lymanhurst, we believed, was protected. In 1931 he died of widespread tuberculosis. A group of fourteen nurses came to us from a small hospital; one was negative. She now has consumption while the others are free. We had a group of medical students who were infected while attending on the tuberculosis service. It is alarming how many become infected. One student who became infected was convinced he was better off. He went to California where he completed his interneship, and about three weeks ago he had a hemorrhage. That was a benign dose. If we follow these cases, repeatedly we find more and more coming down with consumption. We are absolutely convinced from our experience that we should interpret a positive tuberculin test as a liability rather than an asset.

DR. SCHICK.—I would like to ask Dr. Stewart how he feels about Dr. Heimbach's experience abroad. The nurses who came to his hospital in Oslo were divided into two groups, those reacting positively to tuberculin and those who did not. The incidence of active tuberculosis in the nurses of the first group was definitely lower than in the nurses of the second group, all of whom came from the country with negative tuberculin reactions. Subsequent to this experience Heimbach employed B. C. G. vaccination in unprotected (negative tuberculin) cases.

DR. STEWART.—I think Dr. Heimbach is wrong. We have seen the same thing in Minnesota. We are now permitting nurses with primary tuberculosis to keep on with their work. Medical students are permitted to continue on in school with one lobe solid with tuberculosis.

DR. L. L. BIRNBERG (ST. PAUL, MINN.).—I wonder if the old adage "circumstances alter cases" cannot be the cause of the differences of opinion. Tuberculosis has an historical basis. We know there are peoples in Europe who were exposed to tuberculosis for centuries, people who were concentrated and lived in very unhygienic surroundings in populated towns and cities. These people, especially the Jewish people, have had tuberculosis repeatedly for centuries and now find themselves more immune to tuberculosis. The same thing can be said of all old races with old civilizations who still live under adverse circumstances and who survive to develop a relative immunity to tuberculosis. As a rule a positive tuberculin reaction in these people is an asset and not a liability. Now, in Minnesota we have a different people. There we have a young civilization, a young Nordic race that has essentially lived away from the crosses of civilization and the diseases of civilization. Scandinavians contracting tuberculosis usually develop glandular or bone tuberculosis. They seem to have no resistance to tuberculosis, in this resembling the Indian. When an Indian contracts tuberculosis, it goes bad with him because he has had no previous contact with the disease. These facts may explain why the physicians working in Minneapolis have had such bad results with positive tuberculin tests. Their bacilli have grown on fresh, untreated soil which has not had the benefit of any "allergic education" in the past.

DR. STEWART.—At the National Tuberculosis Association meeting this year the question of races was brought up and upset. It has been shown it is more a case of environment, social background, and cleanliness. If the white races sank to the same level, they would have the same thing. The same thing has been proved in California with the different races. No one can prove immunity according to the

generation. We think they react more or less alike. We think something besides active immunity is the explanation. If there is any racial difference, it is not a factor of major importance.

DR. HENRY H. PERLMAN (PHILADELPHIA, PA.).—I would like to come to the defense of atropine as an antispasmodic in the treatment of asthma. I do not know why Dr. Peshkin is so opposed to its use. If there is any drug one commonly uses in pediatric practice, it is atropine. It is a drug that is subject to very rapid deterioration. One of the reasons we do not get satisfactory results from atropine is because it is not properly prescribed. It should be prescribed in not more than one fluid dram vials. For this purpose it should be prescribed in dilute form. In the stomach the effect is not the same as one gets in the throat, the drying of the mucous membrane, or in the dilatation of the pupil of the eye along with the marked dryness and redness of the skin. In the stomach the effect of atropine is much less. I think that is one reason why Dr. Peshkin did not get his antispasmodic effect in the treatment of asthma.

I think a drug that is overlooked with reference to inducing stimulation of secretions in bronchial asthma is sodium citrate. I believe sodium citrate is the best remedy to stimulate secretions in the first stage of asthma. I fully agree with Dr. Bradley in his criticism of the drugs used in bronchial asthma.

DR. PESHKIN.—I quite agree with the statement that atropine is one of the most commonly used drugs in pediatric practice. Because of the fact that atropine is so widely used must one accept this usage as a criterion of its efficacy in all the conditions in which the drug is employed? Asthma, to be sure, is one of the conditions met in pediatric practice in which atropine has been and for that matter, still is, empirically employed. My remark concerning the value of atropine was solely confined to its use orally in bronchial asthma, a condition quite apart from the nonsurgical form of pylorospasm in which the antispasmodic action of the drug is conceded.

A correlation between the pathology of asthma and the pharmacotherapeutics of atropine will bring out clearly the obvious dangers and limitations attendant upon the use of this drug in asthma.

The pathology of bronchial asthma involves other tissues besides the smooth muscles of the bronchial tubes. The necropsy studies made by Huber and Koessler are of outstanding importance. These studies have indicated that the pathologic findings may be divided into two groups. In the first group there is a marked hypertrophy of the bronchial muscles. In the second group the chief lesion consists of a marked swelling of the epithelium with hypertrophy of the mucous glands. The distended epithelium, which is usually intact, is thrown into shallow folds so that occlusion of the bronchial lumen by a further swelling of this thickened membrane easily occurs. Eosinophilic infiltration occurs in both groups. These authors in correlating their findings at necropsy with the clinical course of asthma have concluded that in these cases in which the asthma was uncomplicated by infections and depended upon some inhalant allergens, the main lesion was an hypertropy of the muscles. In the other cases of the bacterial type, the important lesion was the hypertrophy of the mucous glands. In some cases mixed findings were present just as they occur clinically.

The pharmacologic action of the usually prescribed doses of atropine depresses the parasympathetic endings. Aside from its action on the cardiovascular system, atropine "leads to dilatation of the bronchi," relaxation of the stomach and bowel, and lessened secretion of the salivary and other digestive glands. Secretion of the tears, sweat, and mucus are inhibited. Atropine has been empirically used to relieve the paroxysm of bronchial asthma, and its action in suppressing secretions

renders it useful in coryza, night sweats, excessive salivation, etc. No mention is made in the books on pharmacotherapeutics that, while atropine is supposed to relax the bronchial muscles, it at the same time dries up or inhibits the production of mucus. As a matter of experience the usual dosage of atropine employed in pediatric practice has not been uniformly successful in even specially selected cases in relaxing the bronchial muscles sufficiently to cause relief from an attack of asthma. Increased dosage merely intensifies its inhibiting action on the secretions. Were it not for the "double-edged sword" action of atropine as far as the majority of cases of asthma is concerned, there might have been a safe place for its use in asthma. If for the sake of argument, it was always possible to differentiate from the onset an attack of asthma due only to allergic exposure from an attack of asthma due to allergy superimposed by an intercurrent infection, the use of atropine in the first instance would be permissible. However, the action of atropine to relax the bronchial muscles could not always be relied upon unless large and dangerous doses were employed. Its action to dry up the secretions which collect in the bronchial tubes even in the absence of infection can always be relied upon. Since the introduction of the oral administration of ephedrine and its present easy availability and dependable action in controlling mild attacks of all types of asthma, it is becoming more and more apparent that the use of atropine in asthma will eventually be discarded. The question of deterioration of atropine when in solution has been known since Dr. Haas, many years ago, brought these and other peculiarities of the drug to light.

Sodium citrate may possibly be efficacious in the first stage of a bronchitis or during the first days of the attack of asthma. However, I have had no experience with the use of this drug as a stimulating expectorant.

DR. BIRNBERG.—Dr. Peshkin in his talk did not lay special stress on food in asthma. However, I thought the inhalants played a more important rôle in the etiology of asthma than the food proteins.

The second question is, "Has Dr. Peshkin had any experience in the use of a group of foods that have a tendency to cause ketosis?"

Lastly, he spoke of sinus infection as being a secondary factor of allergy and if so has he found it necessary to treat the nasal condition surgically to get relief?

DR. PESHKIN.—Dr. Birnberg has asked three important questions.

It is well known that food sensitization plays a more important rôle in children than in adults but is secondary in importance to the part played by the inhalant group in the causation of asthma, except during the first two years of life when allergic symptoms are almost entirely due to foods and occasionally to an inhalant and to contact offenders such as wool or silk. All children older than two years exhibiting cutaneous reactions to food proteins also react positively to one or more of the inhalants, while the reverse is not true. Food sensitization in children with asthma mostly takes place prior to the seventh year. Children tested for the first time to inhalants show that the average number of reactions per patient is found to be about the same for all ages, and the children so tested for food proteins begin to show the phenomenon of natural desensitization after the eighth year. Natural desensitization with the inhalants, however, does not occur so readily. Negative cutaneous reactions in the presence of positive clinical histories of allergy are much more frequent with foods than with inhalants. Clinical disturbances which develop one or two days following the ingestion of a food are uncommonly associated with positive cutaneous reactions to that food whereas symptoms coming on within a few minutes to a few hours usually show a positive cutaneous reaction to tests with that food. In patients suffering with asthma and associated allergic syndromes, many of the food intolerances encountered are frequently referable to allergic syndromes other than asthma. Finally, it often happens that a patient will be unable to

tolerate a food to which he is sensitive while exposed to the concurrent inhalant, but on the removal of the inhalant substance the same food may be readily tolerated.

In 1930 Dr. A. H. Fineman and I published a paper on the rôle of the ketogenic and low carbohydrate diets in the treatment of a selected group of children with chronic bronchial asthma. At the end of the third week of treatment with the dietary regimen, which involved a maintained and maximum ketogenic-antiketogenic ratio of 3:1, 93 per cent of the children manifested moderate to marked improvement or relief from asthma. These improved states were only temporary, the periods of relief ranging from two to ten months. The various foods known to cause symptoms of allergy were eliminated from the ketogenic diets because, when they were ingested even during the state of definite ketosis, allergic symptoms ensued. For this reason ketogenic diets should not be confused with elimination diets. The ketogenic diet has been of no value in relieving patients from pollen asthma or hay fever. The ketogenic diet, on account of its extreme formula, is a dietary "stranger" to the allergic person and, in our opinion, may be considered, for children, as a form of nonspecific treatment capable of inducing physiochemical change via the alimentary tract.

It is well to repeat that in children with asthma the presence of "sinus disease" invariably denotes a complication of asthma. Only conservative treatment is advised while nasal surgery should be avoided.

DR. LEE F. HILL (DES MOINES, IA.).—What is the number of skin tests with which children should be tested? There are somewhere around 400 such tests. Do you think sixteen or eighteen would be sufficient? Against what substances do you desensitize children?

DR. PESHKIN.—We are opposed to the practice of testing every patient with all available allergens, for it is an unnecessary waste of time and materials. The allergens that are of sufficient importance to warrant their use in a routine manner number from seventy to ninety. The employment of additional tests can be determined from the history, diet, and environment of the patient.

Children are desensitized or rather hyposensitized by inoculations against the common inhalant substances such as pollen, dust, feathers, and emanations from domestic animals when avoidance of the offending substance cannot be accomplished. Food desensitization is best accomplished by restricting the food from the diet over a long period of time; or by feeding gradually increasing amounts of the offending food. Urbach's specific "propeptans" may be given a trial.

DR. ARTHUR W. KIMBERLY (WORCESTER, MASS.).—I would like to ask Dr. Peshkin where I could send a mother and a child on the eastern seaboard during three weeks in the spring of the year when their asthma is troublesome. The mother reacts strongly to alder and the child to dandelion.

DR. PESHKIN.—Alder (Alnus) belongs to the tree family. There are nine species found throughout the United States. In the eastern states are found smooth alder (A. Alnus). These pollens average about 24 microns and are wind borne. Alder belongs to the Betulaceae family and are thus related to birch, hazelnut, and blue beech, in which event the symptoms of your patient may commence about the end of March and continue on through April to about mid-May.

Dandelion (Leontodon taraxacum) belongs to the weed (Compositae) family, produces a small quantity of pollen, is widely distributed, and pollinates in late spring and early summer. The pollen averages about 45 microns, is insect borne, and therefore is not a direct cause of pollen allergy, although it can cause transient symptoms by direct inhalation.

From the clinical history it appears that your patients are sensitive to tree pollens. In the case of the mother, alder sensitivity alone would indeed be a rarity. In the

case of the child, further testing with all the tree pollens will probably bring out the etiologic factor. The important trees causing pollen allergy in the spring are oak, hickory, birch, ash and beech; of secondary importance are the elm, poplar, maple, walnut, sycamore and alder. Freedom from exposure to the pollen of trees is best obtained by an ocean voyage.

The pollinating period of the various trees is as follows:

Oak—from end of April to early June
Hickory—last week in May to about mid-June
Birch species—from last week in April to about mid-May
Ash—from early May to the third week in May
Beech—first two weeks in May
Elm—from end of March to mid-April
Poplar—from April 13 to 26.
Walnut—from last week in May to first week in June (related to hickory)
Alder—from end of March to about April 8.

The meeting was adjourned.

Comments

THE Round Table Conferences held in Cleveland have become a problem for the editors. In previous years a single conference was held and the discussion could be condensed into a report of reasonable length for publication. In Cleveland each Round Table was held twice. The leaders have attempted to unite the minutes of the two sessions into one proceedings and eliminate repetition. Even with this the final reports received for publication are so long that they would take up a disproportionate amount of space in the JOURNAL. It has therefore been necessary to edit and delete the minutes. In doing this the names and remarks of some speakers have been omitted when practically the same thought or idea was expressed in both sessions. The Editorial Board feels that the publication of original articles should not be cut down to make space for the unusual situation which developed this year from repeating the Round Table Conferences.

In connection with the subject of editorial policy, a few words concerning case reports are apropos. A large number of case reports have been submitted for publication, and during this last year it has become necessary to limit the number which can be accepted. Only reports which present some new feature which adds to the knowledge of a condition or disease are approved for publication. Rarity in itself does not as a rule make a case report acceptable. Simply adding one more case to those on record is of little value unless the report adds some new fact or throws light on some controversial or uncertain feature of the condition. As a general rule, manuscripts which consist of a single case report with a long review of the literature citing all previous cases are not acceptable.

Frequently some interesting or unusual case will appear in the practice of some man who quite rightly will make a thorough study of the literature for his own information. This does not necessarily justify the appearance of the study in print. Not infrequently a case report will appear with the statement that the condition is exceedingly rare, as only sixty-odd similar cases are on record. Reference to hospital files will show many more cases which have not been reported, as the study of these cases had added nothing new to the knowledge of the condition. Infrequency of reported cases does not necessarily mean rarity. Case reports which present some new feature of therapy or diagnosis or pathology, for example, are as a rule acceptable by the Editorial Board.

The Editorial Board again wishes to state its disappointment in regard to the news and notes furnished by the State Chairmen. Personal notes in regard to hospital changes, appointments, meetings, and the like are always of interest. The "News and Notes" department, however, can only be made of interest by the cooperation of State Chairmen.